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CONTENTS

PAGE

THE PHYSIOLOGICAL EFFECTS OF RADIATION. *Henry Laurens* 1

THE PHYSIOLOGICAL EFFECTS OF ROENTGEN RADIATION UPON NORMAL BODY TISSUES. *Stafford L. Warren* 92

INDUSTRIAL FATIGUE IN RELATION TO ATMOSPHERIC CONDITIONS. *H. M. Vernon* 130

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PHYSIOLOGICAL REVIEWS

Tentative Contents of Volume VIII, 1928

KENNETH J. FRANKLIN: Physiology and pharmacology of veins
CHARLES C. MACKLIN: The physiology of the bronchial tree from the anatomical viewpoint
S. A. ASDELL: The growth and function of the corpus luteum
HENRY LAURENS: Physiological responses to light
O. R. LANGWORTHY: The control of posture by the central nervous system
S. L. WARREN: Physiological action of x-rays
J. A. GARDNER: Origin and significance of cholesterol
GEORGE B. WALLACE: Specificity in the reaction of drugs
C. E. FERREE: Color vision
H. M. VERNON: Industrial fatigue
FLORENCE R. SABIN: Bone marrow
L. N. KATZ: Significance of the T wave of the electrocardiogram
H. B. VICKERY AND T. B. OSBORNE: Protein molecule
C. P. STEWART AND G. H. PERCIVAL: Calcium metabolism
B. P. BABKIN: Gastric digestion
HENRI FREDERICQ AND M. LAPICQUE: Chronaxie
DR. AND MRS. EDWARD MELLANBY: The influence of diet on tooth formation
H. S. RAPER: The aerobic oxydases
HERBERT S. GASSER: Muscle contracture
E. V. MCCOLLUM: Isolation of vitamins
ADOLF MEYER: Aphasia
PERCY M. DAWSON: Recent literature on physiological effects of exercise
ROBERT FAHREUS: Suspension stability of blood
JOSEPH HOET: Rigor mortis

PHYSIOLOGICAL REVIEWS

VOL. VIII JANUARY, 1928 No. 1

THE PHYSIOLOGICAL EFFECTS OF RADIATION

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This review is limited to the action of radiant energy on the skin, eye, circulatory system, blood (in vivo) and metabolism, with some final reference to possible modes of action. Among the books and reviews dealing with the subject are: Jesionek (1912), Bernhard (1917), Pincussen (1921), Clark (1922), Rollier (1923), Hausmann (1923), Hill (1924 a), Saleeby (1924), Humphris (1925), Mayer (1926).

Those interested in the biological and therapeutic action of ultra violet, visible and infra red radiations are often discouraged because of inconclusive or conflicting results, and above all because of an inability to more than hint at plausible reasons for the reactions obtained on normal and abnormal animals, organs or tissues. The biologist and clinician, however, should not feel discouraged, for there seem to be but few instances of photochemical effects where the physical process is understood. Furthermore, the lack of agreement between practical and therapeutic results on the one hand and scientific or experimental on the other is due to the fact that the experimental observations have been made for the most part on healthy men and animals, while the practical or therapeutic results have been obtained on diseased persons. The sick organism is a much more delicate mechanism than the well, diseased tissue being more susceptible to radiation than normal, while the animal skin is an entirely different organ from the skin of man.

According to the report of the Committee on Spectrophotometery of the Optical Society of America, which appeared in the Journal for February 1925, *radiation* is the process by which energy is propagated through space. Strictly speaking the term should not be used to express the "thing radiated," but this is commonly done and we shall use the word as synonymous with *radiant energy*, which is that which is transferred by radiation. Like any form of energy it may be expressed in energy units, such as the erg, joule or calorie. *Radiant*

power is the time rate of change of energy by radiation, and it may be expressed in power units such as the watt, designated by the expression *radiant flux*. *Radiant intensity* in any direction from a source is the radiant power per unit solid angle in that direction. If radiant energy be incident upon a surface the irradiation of that surface is the radiant power per unit of intercepting area. *Light* is radiant energy multiplied by the visibility of the radiant energy. The expressions "ultra violet light" and "infra red light" are misnomers. *Light* is that agent, force, or action in nature by the operation of which on the organs of sight objects are rendered visible or luminous. In other words, it is visible radiant energy. Ultra violet and infra red do not render objects visible, and they are therefore invisible radiant energy. Radiant energy is emitted by every substance above absolute zero at the cost of its own heat energy. Such radiation has been termed "pure temperature" radiation, since it depends only on the temperature of the body. When it is due to electrical or chemical processes in part or in entirety it is termed luminescence. The sun, the carbon arc, metal filament lamps, etc., are pure temperature radiators emitting a continuous spectrum, the extent and distribution of which are functions of temperature and hence of the total radiation intensity. Mercury vapor lamps are luminescent radiators, the radiation originating from the atomic and molecular characteristics of the Hg vapor and consequently discontinuous, consisting of lines and bands resulting from the processes going on in the atoms and molecules.

We are now in possession of a great deal of general knowledge pertaining to the effects of radiant energy but somewhat lacking in specific details, especially those pertaining to the spectrum, such as spectral limits, spectral distribution of energy, and spectral character of the radiant energy employed. If the source of radiant energy be fully described and the spectral limits specified this is much more satisfactory and scientific than attributing a result merely to "ultra violet energy." The absence of data pertaining to the source employed is the cause of the contradictory nature of many of the therapeutic and experimental results that have been published.

If a standard arc, such as an iron or carbon arc, be used, such specifications as nature of source, distance from subject and duration of exposure might be regarded as sufficient when apparatus is not available for measuring the energy. But when the Hg arc is used these simple specifications are meaningless. Different Hg lamps vary much in intensity and in the spectral distribution of their energy output. With

use they show deterioration, so that even when the energy input is kept constant, which is not often the case, the energy output is increasingly inefficient, particularly with reference to the ultra violet component. The energy emitted by various artificial sources varies not only in spectral distribution but also in intensity as to wave length so that comparisons of results obtained with different sources can at best be only very general and superficial unless the total radiant energy as well as that of the various spectral subdivisions is specified in absolute units. The intensity of solar radiation is a very variable factor, varying momentarily, daily, seasonally, and geographically. Furthermore, the amount of radiation which reaches the earth's surface is dependent upon every change of atmospheric transparency, dustiness, humidity, and so forth. A rigorous comparison of results obtained with solar radiation by different investigators at different times and places is practically impossible, as is a comparison of results using the radiation from artificial sources, unless the energy is specified in absolute units. There is frequent, more often than not, lack of radiometric measurements, although there are many statements regarding equal intensity, etc., with no information as to what is meant.

If artificial phototherapy is trying to imitate sunlight it behooves workers with artificial sources to know something about the physics of sunlight, as well as of the radiation of the lamp they are using. Radiation can be completely specified by two things: the total radiation present and the spectral distribution of the energy. But wave length does not accurately define the properties of radiant energy. Ultra violet, visible and infra red radiation can all be shown to have chemical effects depending upon the process, although for many the ultra violet rays are much more effective. Similarly all the wave lengths included within these limits can be measured as heat energy by causing them to be absorbed on the surface of a thermopile. The aggregate spectrum of sunlight is thus its heat spectrum.

There are a number of authors (Abbot and co-workers, Dorno, Kimball) who have given us information concerning the intensity of solar radiation and its variations, and we are very much better informed regarding sunlight than we are about its substitutes. The importance of sky radiation is very generally ignored. It is evident that the beneficial effects of sunlight are in great measure due to its luminous and infra red portions, as Rollier, Dorno and others hold. Dorno shows that sky radiation at Davos contains, in contrast to the rest of the spectrum, from two to four times more ultra violet shorter than

366 mμ than does direct sunlight. Abbot also demonstrated that on Mt. Wilson skylight was several times richer in violet and ultra violet than was direct sunlight, while Tisdall and Brown find that December skylight in Toronto has an antirachitic effect almost as marked as that obtained by exposure to the available sunlight.

Solar radiation as it reaches the earth extends from 290 mμ to 5 μ although there is but very little energy longer than 2 μ, and it is often described as extending from 0.3 μ to 3 μ. On entering the earth's atmosphere 5 per cent of the total radiation (1.93 g. cal. per sq. cm. per min.) is ultra violet, 52 per cent visible, and 43 per cent infra red. Owing to extinction and absorption by the time the radiation reaches the earth's surface the relative amounts have changed and at average heights of the sun with a total radiation intensity of 1.0 g. cal. per sq. cm. the distribution is ultra violet 1 per cent, visible 40 per cent and infra red 59 per cent. Total intensity is primarily dependent upon height above sea level, as well as upon seasonal and daily variations, which particularly influence the ultra violet. Abbot shows that only 75 per cent of the total solar radiation (the solar constant) reaches a level of 1800 meters, and only 50 per cent to sea level. Spring sunlight is the strongest and richest in infra red, the autumn sun by comparison being richer in ultra violet, the maximum content of which is reached in the summer.

There is very little known concerning the details of tropical solar radiation. Knipping finds that the radiation intensity per unit time in many tropical places differs very little from that of places in the temperate zones in clear weather in the summer time. The great difference lies in the total radiation which shows large daily and annual differences, particularly in the short waved fractions. In many tropical towns in the British and Dutch Indies near the coast in low lying country with high humidity and much dust the maximum intensity is not as great as is experienced in June at midday on the North Sea coast. Similarly in spite of few clouds and with low humidity the intensity of many places in the Red Sea region and in Arabia is, on account of the dust, surprisingly low. Knipping finds that at many tropical places the ultra violet does not extend as far as 290 mμ and that at many other places, high and with relatively low humidity and little dust, the spectrum extends farther and is more intense than in the Alps. Thus tropical sunlight can be used therapeutically with safety, but although, as far as the heat rays are concerned, the amount of radiation in a unit of time is not much greater in the tropics than at midday on a clear

summer day in Germany, the other climatic conditions (temperature, humidity, etc.) permit a much smaller loss of heat in a unit of time, so that there is menace from loss of heat balance. According to Sundstroem any ill effects from insolation in the tropics are due to the absorption mainly of longer rays and to a resulting failure of the heat regulation. The trend in newer contributions to tropical physiology seems to be to minimize the action of "actinic rays" and to focus attention on a continuous reduction of cooling power.

Choice of source. Of the available sources the sun, the Hg arc in quartz and the C arc, burning solid or cored carbons filled with mixtures of rare earths, are the only ones of practical importance, though iron and tungsten arcs have also been used in experimental work. The common belief that the radiation of such sources is solely or mainly active because of the ultra violet fraction may be so, but it has been demonstrated in only a very few instances, such as the cure and prevention of rickets, and the formation of melanin in the skin. On the other hand there is much evidence that the effects observed are due to the entire spectrum. In some cases the evidence points to the visible portions as being particularly active (Sonne, Loewy and Dorno, Saleeby, Balderrey and Ewald, LoGrasso and Balderrey). In others the action of certain wave lengths in the ultra violet has been shown to be increased by the simultaneous action of the visible and infra red (Hill). The appreciation of this is demonstrated by the placing of a cluster of incandescent lamps around the hood of the quartz Hg lamp.

Humphris thinks the mercury lamps are suited to superficial conditions, the C arc to more deeply seated maladies and systemic pathological conditions; a view based on the greater penetration of the visible and infra red rays of the C arc. For the general body bath he prefers the C arc to the quartz Hg lamp, because the rays from the former are more like solar radiations than those obtained from any other source. Malten regards natural sunlight, even at sea level, as the method of choice, no other source approaching it in effectiveness, with the C arc lamp next owing to its similarity to the sun, but only for local treatment, while for total irradiation, which is preferable to local, the quartz Hg lamp must be used, a view opposed to that of Humphris. Reyn calls attention to the greater penetration of the rays of the C arc, and the production by them of a strong red-brown pigmentation in contrast to the blue-red color produced by the Hg lamp. Sonne also prefers the C arc, particularly because of its richness in luminous rays which he regards as most effective since they penetrate to the deeper regions

and warm them, unlike the outer heat rays and ultra violet which are absorbed in the outermost layers of skin. Mayer, however, believes that the only basis for the insistence on radiation having a spectrum closely resembling that of sunlight is that results with solar exposure have been most favorable in the hands of these workers. He holds that there are sufficient grounds for expecting therapeutic results with other combinations of light rays, for example, certain forms of tuberculosis respond more readily to sources of great intensity in ultra violet radiation than to solar radiation.

We may take the broad view that work with all the various sources will yield results of interest and importance but that investigators and clinicians should know what they are doing, what wave lengths they are using, the total intensity of the energy and its spectral distribution. This they should do in preference to describing as "ultra violet" the total radiation from the lamp and ascribing to "ultra violet" the effects produced.

Several investigators have called attention to the deterioration with use of Hg lamps. Coblentz and his co-workers established that the ultra violet rays emitted from air cooled quartz Hg vapor lamps decrease from an initial value of about 70 per cent of the total radiation of wave lengths less than 1.4 μ (30 per cent of the total radiation of wave lengths emanating from the whole lamp) when the lamp is new to about 50 per cent after 1000 to 1500 hours' usage, with no marked difference noticeable in the first 500 hours. The total radiation decreases in intensity by one-half to one-third the initial value in the course of 1000 to 1200 hours. The new Hg lamps do not deteriorate so rapidly (Coblentz, Dorcas and Hughes).

Nature of spectra. Spectra are of three classes, continuous, banded and discontinuous or line. The sun's spectrum is a continuous one, extending from about 290 mμ to 5 μ. The spectrum of Hg vapor in quartz is discontinuous (strong emission lines on a background of a weak continuous spectrum), the shortest lines getting through the quartz and air being 185 mμ. The spectrum of the ordinary C arc gives a groundwork of a mass of fine lines with bright lines from the spectrum of the various impurities in the carbons, especially Fe and Ca. The white flame C arc spectrum consists essentially of two, a line spectrum from the metals added to the carbon, the radiation of the arc vapors, upon which is superposed the continuous spectrum of the incandescent positive crater. It extends from 218 mμ, though most of the energy is at wave lengths longer than 290 mμ, to the neighborhood of 6 μ.

Methods of measurement. Various methods are available for measuring and specifying radiant energy and its spectral distribution, but practically they reduce to three, Thermo-electric measurements, Chemical reactions, and Discharge of electrons. Coblentz and his co-workers have described the instruments and methods of radiometry, and Gibson and his co-workers the use of the spectrophotometric method. Abbot and Dorno have described particularly the methods for measuring solar radiation (see Gorczynski). In addition to various pyrheliometers Dorno advocates the use of the cadmium photo-electric cell for measuring the ultra violet on account of its great sensitivity in this region, and considers it the instrument of choice for the measurement of sky radiation.

Clark (1924) developed a photochemical method for use in clinical and qualitative laboratory work, proposing that the darkening of lithopone paint to a reflection factor of 50 per cent be taken as a unit of intensity of ultra violet. Webster, Hill and Eidinow take the amount of bleaching, found to be proportionate to the length of exposure, of methylene blue in an acetone-methylene blue mixture in quartz tubes as indicative of the intensity of ultra violet. Later, Hill (1924 b) recommended that the standards be made with copper nitrate and potassium chromate. Pfund describes an actinometer of fluorescent uranium glass. Mayer reviews a number of other qualitative methods. Mayerson, Gunther and Laurens use a radiometric method, agreeing with Coblentz that the logical method of procedure is to measure the intensity of the radiation in absolute units by using a non-selective radiometer, such as a thermopile and galvanometer, which can be calibrated by means of a standard of radiation. The following outline represents what should be done in measuring and specifying radiation for physiological uses. Spectrograms are made so that the general character of the spectrum, its wave length distribution and limits, are known. The responses of the thermopile are converted to C. G. S. units, by calibrating it against a radiation standard. We use a thoroughly seasoned Bureau of Standards carbon lamp, the radiation intensity of which per square millimeter at a certain distance, say 2 meters, when operated at a stated amperage, according to instructions furnished with the lamp, is certified. The current sensitivity of the galvanometer is ascertained by passing through its coils a current of known strength. After the standard current sensitivity of the galvanometer is thus obtained any deviation from this is corrected for. The sensitivity of the radiometer (thermopile and galvanometer) is

ascertained by exposing the thermopile to the standard lamp. Then, knowing the radiation intensity in watts per sq. mm. at the distance, the current sensitivity of the galvanometer, the sensitivity of the radiometer and the area of the sensitive receiving surface of the thermopile, it is possible to assign to a galvanometer deflection of, for example, 1 cm., a value in terms of energy incident per square centimeter of thermopile surface. Knowing this, it is a simple matter to compute from the size of the galvanometer deflection, the energy emitted by any source at any distance in g. cal. per sq. cm. per min. We have in this manner determined the total energy of two flaming arc lamps burning ½ in. cored white flame carbons. In the "Solarlite" (25–28 A, with a potential drop of 40–50 V across the arc) it is 0.912 g. cal. per sq. cm. per min. at 40 cms; and in the "Pan-Ray-Arc" (25–28 A, with a potential drop of 60–65 V across the arc) it is 1.0 g. cal. per sq. cm. per min. at 103 cms.

The percentage distribution of the energy was determined by two methods: 1, by using a screen with an approximate cut off at 400 mμ and a quartz water-cell with an approximate cut off at 1.4 μ; and 2, by the dispersion method, using a quartz monochromatic illuminator and a rock salt infra red spectrometer. The energy of the "Solarlite" is distributed as follows: ultra violet 22 per cent, visible 43 per cent, and infra red 35 per cent; and of the "Pan-Ray-Arc" 15 per cent, 59 per cent and 26 per cent respectively.

Comparison with other sources shows the importance of this specification. An air-cooled quartz Hg lamp has a spectral distribution about as follows: 30 per cent ultra violet, 53 per cent visible, and 17 per cent infra red. In the water cooled lamps the ultra violet equals the visible. Sunlight at sea-level contains from 1–2 per cent ultra violet, 43–53 per cent visible and 57–43 per cent infra red. Sunlight on Mt. Wilson contains from 2–5 per cent ultra violet, 50–55 per cent visible, and 48–40 per cent infra red; and on Mt. Whitney, 3–6 per cent ultra violet, 54–55 per cent visible, and 43–39 per cent infra red. The differences between the spectral distribution of the energy from the various sources is obvious.

Another form of comparison is even more striking. If the total intensity of the "Solarlite" is compared with Coblentz, Long and Kahler's average of solar radiation intensity for several days in Washington the values will be found to be practically identical, 0.0154 g. cal. per sq. cm. per sec. for the lamp, and 0.0155 for the sun. But, as above shown, the distribution of the energy is quite different. Coblentz

and Kahler show that for three hours at noonday the average seasonal solar radiation may be taken at 1.2 g. cal. per sq. cm. of normal surface. Of this from 1–2 per cent is in the ultra violet shorter than 390 mμ or about 0.02 g. cal. per min. per sq. cm., and usually it is perhaps about one half this value. In comparison a quartz mercury vapor lamp at a distance of 40 cms. from the burner has a radiation intensity of 0.0017 g. cal. per sq. cm. per sec. About 30 per cent of this radiation is in the ultra violet of wave lengths shorter than 390 mμ, which would give about 0.0306 g. cal. per min. per sq. cm. for a new lamp, decreasing after some usage to about 0.02 g. cal. per min. per sq. cm., or the same as obtained from solar radiation. But the spectral quality of this ultra violet is quite different, that of the sun terminating at 290–300 mμ, while the Hg arc may emit wave lengths as short as 185 mμ. Carrying the comparison just a step farther: the ultra violet component of solar radiation of wave lengths less than 300 mμ is less than 5 per cent of the total ultra violet component. In the quartz mercury arc it is 20 per cent of the total ultra violet component.

Coblentz (1925) has recently compared carbon and quartz Hg lamps with the sun, as to wave lengths emitted and the percentage distribution of the energy between 170 mμ and 1.4μ. It seems a pity that the energy in the longer infra red, as it occurs in the solar and C arc spectrums, was not evaluated. Coblentz points out that there can be no exact comparison of the radiometric measurements or the therapeutic results of the ultra violet and luminous rays from the sun, C arc and quartz Hg lamps because they are at different temperatures and have different spectral radiation components. In two later papers (1926, 1927) he gives data on the distribution of energy in the spectrum of the C arc under varying conditions of operation, with comparisons of the sun, Hg lamp, etc. The spectrum was divided into seven parts by means of a quartz spectroradiometer. The lines of division, particularly at the boundary between ultra violet and visible and between this and the infra red, make it difficult to compare the results with other work.

The value of measuring radiant energy is particularly well demonstrated by the work of Verhoeff and Bell and of Coblentz and Fulton in which the energy relations are correlated with biological action.

Effects on the skin. *Penetration.* The skin is the means through which radiant energy acts on the organism and the changes taking place in it during and after irradiation deserve careful consideration. Its penetration has been studied, though not very accurately so, in

that the values given are for skin from some particular region and therefore of only relative value. The reflection and penetration of the skin is very different for different parts of the spectrum as well as for different parts of the body, and pigment, hair and blood are all important elements in determining the relative amount of energy absorbed and distributed. von Brunn gives the thickness of the epidermis in various parts of the body. Over the papillae on the forehead it varies between 0.06 and 0.09 mm., on the cheek between 0.06 and 0.1, on the neck, arm, abdomen, back and leg between 0.04 and 0.1. Between the papillae it is thicker. The dermis in most parts of the body is between 1.7 and 2.0 mm. thick.

We know that the luminous rays, particularly the red, are capable of passing through several centimeters of the human body (Hausmann p. 78, Jesionek, p. 336 and Balderrey and Ewald). Freund showed that epidermis from blisters absorbed everything shorter than 325 mμ, while hardened scales of skin absorbed everything shorter than 344 mμ when yellow, and shorter than 329 mμ when colorless. The frog's web in which blood is circulating absorbed wave lengths of sunlight shorter than 397 mμ. Until Hasselbalch's work nothing was known as to how much radiation of different wave lengths penetrates the skin. Hasselbalch used the skin from the chest of adults and infants after showing that living and dead skin (albino rabbit) showed no measurable differences. He called attention to the fact that pigment and the amount of circulating blood affects the results so that his average values are deceptive, and the absorption coefficient derived for the skin of the chest would have to be increased in order to apply, for example, to the skin of the face. He employed the Kromayer water-cooled quartz Hg lamp and determined the relative transmission spectrographically. The absorption coefficient for various wave lengths from 436 mμ to 313 mμ was ascertained for different thicknesses of skin and durations of illumination and from this the transmission of 0.1 mm., 0.5 mm. and 1.0 mm. thick skin for wave lengths 436 to 298 mμ was calculated. One millimeter thick skin lets through only 0.3 per cent of the incident energy at wave length 405 mμ and 0.006 per cent at 313 mμ. Skin 0.5 mm. thick lets through 5 per cent and 0.3 per cent respectively at these wave lengths, while 0.1 mm. thick skin lets through 55 per cent at 405, 30 per cent at 313, 2 per cent at 297, and 0.1 per cent at 289 mμ. Hasselbalch's tables are reproduced in Hausmann (p. 81) and in Clark (p. 282). Glitscher continued the work of Hasselbalch into the visible and plotted a curve from the ultra violet to the red which shows that wave length and penetration proportionately increase.

Von Schubert criticizes Hasselbalch's methods. Aside from the difficulty of accurately comparing the density of two separate photographs, Hasselbalch on the basis of the absorption of a certain thickness of tissue determined it by calculation for others. Owing to the non-homogeneous nature of skin, to the fact that it is composed of various layers of different nature, von Schubert questions the applicability of the method, although as Hasselbalch demonstrated it may hold for layers of blotting paper.

Barr and Bovie point out that the absorption curve of protoplasm (amoeba) is low for wave lengths longer than 320 mμ, rises abruptly to a peak at 280 mμ, descends quite as abruptly to half its height on the short wave length side, with a minimum at 250 mμ, and then rises again with extreme abruptness to very high values in the shorter wave lengths. The absorption coefficient varies from 200 for 238 mμ to 1000 for 200 mμ.

Macht, Bell and Elvers claim that the penetration through the skin of rabbits, cats and dogs of ultra violet rays from modern quartz Hg lamps is much greater than has been generally supposed. But it is evident that if an intense enough source and a long enough period of exposure be used, much deeper and denser tissue even than that cited by Macht could be penetrated (Mayer, p. 102).

Sonne decides that the evidence at hand does not permit us to say that the beneficial action of irradiation is to be found exclusively in the ultra violet region. He made very careful determinations of the amount of visible and of inner and outer infra red rays which could be borne by the human skin and found them in the ratio of 3.11 to 1.79 to 1.33. Owing to reflection the quantities absorbed were in the ratio of 2.02 to 1.16 to 1.33, the figures being in g. cal. per sq. cm. per min. During irradiation with the highest endurable intensity of visible energy the skin temperature rose to 43.8°, with outer infra red to 45.5°C. Fifteen seconds after irradiation the relation is reversed, the skin temperature after irradiation with visible rays being 1°C. higher, indicating that the subcutaneous temperature is greater during the irradiation with the visible wave lengths. By calculation and actual experimentation with a needle thermocouple Sonne showed that the temperature of the tissue during irradiation with outer infra red gradually falls from 45.5° at the surface to 37° at 1 cm. depth. For visible rays the maximum temperature at 0.5 cm. depth is 47.5°C., and during exposure to outer infra red the temperature at the same level is 41.7°C. At a depth of 1.2 mm. the temperatures are identical, namely, 44.6°C.

The inner infra red rays penetrate somewhat farther than the outer and thus the temperature slightly below the surface is somewhat higher than the surface temperature.

Sonne believes the heating by the luminous portion of the heat spectrum of subcutaneous tissues and the blood therein to temperatures greater than those experienced in fever, but without raising the general body temperature owing to the heat regulating mechanism of the body, to be the main feature of the curative action of radiant energy, and it is for this reason that he favors the C arc over the quartz Hg lamp, which emits far less luminous rays than either the sun or the C arc. Sonne's work has been substantiated and extended by Dorno (1924, 1926b) and Loewy and Dorno.

Erythema and pigmentation. Sunlight is only one of numerous factors which influence and determine the color of the skin of man. Finsen concluded that light has only a minor influence on the physiological redness and later color of the skin of white races, this being more dependent upon the mechanical stimulation of wind, rain and cold air. On the other hand the peculiar pale, yellow-green color of arctic explorers is ascribed to the darkness of the long winter night, and not to cold (Jesionek p. 211, 371). The almost immediate reddening of the skin after irradiation with energy containing ultra violet, visible and infra red rays is due to radiant heat (infra red and luminous rays). This heat hyperemia, frequently mottled, is not restricted to the irradiated parts of the skin and disappears soon after the irradiation. It is followed in a few hours by an erythema due to the action of the ultra violet rays on the cutaneous capillaries. The usually diffuse and homogeneous redness of the erythema is confined strictly to the irradiated part and, according to the intensity of the radiation, may be combined with blistering and hemorrhage. The inflammation lasts for some time, to be followed by peeling and pigmentation. Finsen demonstrated that parts of the arm covered with glass showed when exposed to a strong C arc an early heat erythema, but no later ultra violet effect, while a portion covered by a quartz plate showed the same characteristics as the uncovered arm and became intensely red, hot and sensitive, the erythema lasting for several days, gradually disappearing, the skin peeling and pigmenting. The longer ultra violet, as passed by "clear" glass, as well as the visible violet rays also inflame the skin but very much less so than the shorter ultra violet rays do.

The fact that the ultra violet content of solar radiation increases with altitude, both qualitatively as to wave length (slightly) and

quantitatively as to intensity, together with the strong reflecting power of ice and snow is clearly indicative as to why one is so intensely "sunburned" on high mountains. Not only does the intensity of sunlight increase with altitude, but that of each of its major component parts, the increase in ultra violet being proportionately the greatest, that of the infra red absolutely the least, and relatively obscured by the increases in ultra violet and visible. Dorno finds that the winter sun has a relatively high heat intensity with a minimum of ultra violet. The spring sun has the greatest heat intensity with slightly increased, quantitatively and qualitatively, ultra violet. The summer sun shows a slightly decreased heat intensity with the maximum of ultra violet, while the autumn sun shows only a slight decrease in heat but a marked reduction in ultra violet, though it contains about twice as much as the spring sun. The fact that "glacier burns" occur in winter and that the greatest degree of erythema with subsequent pigmentation is said to occur in the spring has been used to throw doubt on the meteorological findings of Dorno. But in winter and spring the overhead or direct radiation is much increased by that reflected from the ice and snow, and in the spring the skin has usually become unaccustomed to radiation and depigmented by being protected indoors. Thus exposure at this time is followed by marked effects.

"Light" erythema and pigmentation are the results of action of ultra violet, but total solar radiation favorably influences the extent and duration of pigmentation, pigment produced by sunlight being of better quality and lasting longer than that produced by either the Hg or the C arc (Dorno, 1926, Reyn, Sonne). Pigment is formed by the action of the ultra violet in sunlight, so that wave lengths longer than 290 mμ must be effective, while sunlight through glass that cuts off wave lengths shorter than between 320 and 330 mμ produces only a slight degree of pigmentation. Wave lengths shorter than 290 mμ although they produce violent inflammation do not result in heavy pigmentation, being absorbed before they reach the basal epidermal cells. Hausser and Vahle show that the efficient wave lengths for both erythema and pigment formation are in the neighborhood of 300 mμ, and that the two things are very intimately connected, pigmentation following the action of particular wave lengths only when an erythema has been produced, although a slight erythema may occur without subsequent pigment formation. Using lines of equal energy from the quartz Hg lamp they demonstrated a maximum of action for the production of erythema, and later of pigmentation, for the region between 313 and

280 mμ, particularly at lines 302 and 297 mμ. Wave lengths shorter and somewhat longer than this produce a very transitory erythema, lines 334 and 366 mμ having no influence.

The literature is full of references to the difference between the pigmentation produced by sunlight and C arc lamps on the one hand and that produced by the quartz Hg lamp on the other. A tan produced by the sun or the C arc lamp is said to fade when irradiation is continued with the Hg lamp. Reyn, Hausmann, LoGrasso and Balderrey, etc., call attention to the difference in color between the pigmentation produced by the C arc lamp and the Hg lamp, that of the former being similar to sunlight, while that of the latter is a pale, slaty, yellowish red. Dorno reports that sunlight pigment lasts up to 6 months, that of the Hg lamp a month at the most, since only the more superficial layers are affected.

Function of pigment. One of the important functions of pigment is the protection it affords the organism against excessive irradiation, arising as it does as a physiological response to overstimulation. Finsen demonstrated the protective action of pigment by showing that on successive exposures of the arm the pigmented areas were not inflamed, while those previously covered by glass, and thus protected, showed an intense reaction. The skin of mountain dwellers and of sailors no longer reacts to exposure to sunlight which acts painfully on the unaccustomed, unpigmented skin of another. The physiologically highly stimulative action of the spring sun on the skin bleached during the winter is another case in point. Burchardi demonstrated that irradiation no longer influenced the blood picture after pigmentation, and Rothman showed the same thing for the depression of blood pressure and blood sugar and increase in serum Ca. Pigment also offers protection against long waved radiation in cases of photodynamic sensitization, such as the "Buckwheat sickness" of cattle. Black and grey mice apparently cannot be sensitized to light by hematoporphyrin, while white mice can. There is considerable reaction today against regarding the effect of sunlight and the energy irradiated by artificial sources as being solely due to the ultra violet rays. Since dark skin warms much more quickly and thoroughly than does fair skin and holds more heat, pigment may facilitate thermotherapy. Colebrook, Eidinow and Hill, and Campbell and Hill, show that the pigment acts as a screen and protects deeper structures from excessive radiation and converts visible radiation into dark heat. It has no sensitizing effect.

There is no unanimity of opinion as to the therapeutic value of pig-

ment. Many regard it, owing to its absorption, as unfavorable for light action and therefore attempt to prevent its formation (Finsen, Hasselbalch, Reyn, Peacock). Others ascribe to it a very important value (Rollier, Gauvain, Bernhard, Jesionek) and believe that degree of pigmentation is a favorable diagnostic sign, brunettes thus responding better to insolation than blondes. A prophylactic function has been ascribed to pigment, pigmented skin being said to possess a marked immunity to local infection. Acne is said to be rare and the cutaneous vesicles of chicken-pox do not occur on tanned skin (Rollier). Lupus and skin carcinoma occur much less frequently than in non-pigmented skins (Bernhard).

Clark refutes Rollier's theory that pigment by fluorescent action transforms short waves to longer waves of greater penetration. Peacock finds that melanin is non-fluorescent while epidermal keratin, white hair and sebum are. Both melanin and sebum powerfully absorb ultra violet. Fluorescence occurs immediately, while pigment takes time to develop, and therefore fluorescence offers a more immediate protection against ultra violet. Fluorescence and pigmentation vary inversely and pigment therefore is the evidence of failure of fluorescence to sufficiently protect the structures of the cutis vera from excessive radiation. The deliberate production of pigment is tantamount to producing a natural and efficient protection against the treatment. Saleeby thinks that pigmentation may represent in part the power of response to radiation and that the absence of pigmentation indicates a failure of that power. According to Reyn while pigmentation is usually an index of the progress of treatment it is not necessary to the cure, and the best results are obtained when a strong erythema is produced. Malten, on the other hand, considers erythema as having nothing to do with therapeutic action, while Hasselbalch and Jacobaus regard skin hyperemia, with its modified distribution of blood such that a greater amount comes to the vessels of the integument, as the real aim of many therapeutic measures. Bang regards pigment formation as important because it removes harmful substances from the body.

Dorno (1924, 1926) made an interesting comparative study of the relative signs of pigmentation in 25 subjects of different race, age and sex, following exposure of the inner surface of the upper arm to a known amount of sunlight, the ultra violet content of which was determined by a cadmium cell. Fourteen of the subjects were also irradiated by a quartz Hg lamp. Colored races (Indians, Malays and Chinese) react most strongly, and blondes the weakest. Red-haired persons

exhibit a very transitory erythema. Children and youths are more sensitive than adults. Erythema is always followed by pigmentation, except in red haired persons, and pigmentation without previous erythema does not occur. The reflecting power of unpigmented skin is greatest in red, least in yellow, and a little greater in green. The relative values for pigmented skin are similar, but it reflects much less than unpigmented does, the red showing the least difference. The loss occasioned by pigment is much greater in the yellow and the green than in the red. The greatest loss in the red rays takes place in red-haired and light blondes. The maximum absorption in the yellow is an adaptation to natural sunlight, the maximum intensity of which is in this region, and pigment protecting the body from an overdose of the most intense rays is thus a regulator. These wave lengths are held back by the pigment, transformed into heat in the skin from which it is easily given off and particularly in the cool dry air of high altitudes. Herein, according to Dorno, lies the explanation for the increased tolerance which accompanies pigmentation. If we remember that the winter and spring sun is richer in the more penetrating shorter waved infra red and visible rays than is the autumn sun, that in the spring the absorbing pigment has yet to be formed, while in the fall the ultra violet rays are practically at their maximum and pigment is well developed, we have the explanation for the frequent fatigue which occurs in spring, namely the deep penetration of radiation.

Histology of irradiated skin. The changes are briefly as follows: the vessels become dilated with infiltration of the epithelial layer and an abnormal thickening and darkening. Following intense irradiation there is serofibrinous or cell-rich, often hemorrhagic, exudation. If the irradiation is severe enough the collagenous tissue becomes swollen and homogeneous, the epithelium swollen and loosened, infiltrated and blistered, the loss of continuity occurring at the boundary between the granular and horny layers. If the irradiation is quite intense thrombi form in the vessels of the cutis. Irradiation of the ear of rabbits with a powerful C arc lamp results in degeneration and necrosis of the epithelium, blister formation, stasis, fibrinous exudation to the surface and tissue spaces. In addition there is a relatively slight white cell infiltration, mainly of lymphocytes, with plasma cell formation. Finally a marked production of fibroblasts and the formation of new vessels and regenerative processes in the epithelium. The hair follicles and sebaceous glands break down and are regenerated from the epithelium.

Lewis and Zotterman have recently shown that the reactions to injury of cutaneous vessels by ultra violet radiation, as by freezing, burning, etc., are due to the production of vasodilator substances in the skin which diffuse into the surrounding skin and are conducted away by lymphatic channels. Following intense irradiation and other forms of cutaneous injury the vessels are subsequently dilated and the skin becomes edematous. Later the vessels contract imperfectly to epinephrine and pituitary substance, and are more or less refractory to histamine owing to loss of contractile tone.

Origin of pigment. Skin melanin either arises as a substitution product of Hb or *de novo* from nucleolar substances in the epidermis. Ehrmann supported the first view but Meirowsky, Bloch and Lutz, among others, have shown that the formation of pigment is independent of the blood, that it arises in the epidermis and is not brought into it. The color of the skin depends not only upon the amount of pigment but also upon its distribution. Acquired pigment is extracellular, in contrast to its normal intracellular position as in negro skin.

Fürth thought that the origin of melanin was dependent upon the interaction of two fermentation processes, and that protein splitting ferments separated out cyclic complexes from the colorless protoplasm after which, by the action of oxidative ferments, the melanins (products of high molecular condensation) were formed. Bloch's work represents a considerable advance in our knowledge of the origin of pigment. In skin placed in aqueous solutions of Dioxyphenylalanin—"Dopa"—, the development of pigment ranging from smoky grey to deep black was observed. "Dopamelanin" is formed by oxidation and condensation through the specific action of "dopaoxidase," an intracellular oxidation ferment, on the Dioxyphenylalanin, and the colorless precursor of skin pigment is assumed to be something akin to Dioxyphenylalanin. The Dopa reaction does not take place in the white patches of acquired leucodermia (Vitiligo) nor in the skin of albino rabbits, but it is very strong in the skin of negroes (Lutz). Rothman supports the view that melanin, with adrenalin, is a tyrosin derivative.

Action on wounds. Bernhard, "the founder of modern Heliotherapy," tells how he was induced after observing the influence of mountain sun in curing meat to try it on refractory wounds. His success was so striking that he decided to expose to direct sunlight all wounds, frostbites, burns, etc., and to apply the method in cases of closed surgical or extra-pulmonary tuberculosis. The healing action of sunlight is

regarded as due to its total spectrum. Bernhard cites the beneficial action of insolation at considerable depths as exemplified by the behavior of fistulae on bright and cloudy days, showing that it must be the visible and near infra red, owing to their penetrating power, which are effective. The benefit is not due to active damage to microörganisms and their toxins, but to direct stimulation to epithelization. There is an analgesia as well as improvement in local condition, due to hyperemia, as evidenced by copious granulation, dryness and sterility. The dry air of mountains assists insolation but is not the chief factor, since much more rapid healing follows direct insolation than exposure to diffuse daylight. The quartz Hg lamp has some influence on cicatrization.

Coburn and Cowles produced a standard sized wound in rats and exposed them in different series to the radiation of the flaming C arc, the Fe arc, and to sunlight. They obtained no constant difference in the rate of healing from that taking place in rats in darkness or in ordinary room light, though there was some evidence that healing was initiated first, and proceeded most rapidly in the animals kept in darkness, and next in those kept in sunlight. It is possible that the large percentage of ultra violet with little penetrating power emitted by the arcs being absorbed in the most superficial layers of the wound area may have exerted a harmful, rather than a beneficial influence, of the nature of cell destruction, which retarded the rate of healing. Laqueur had considerable success with wounds treated with sunlight, the ideal radiant energy, because it embodies not only ultra violet, which hastens granulation, but also the long waved light and heat rays which penetrate deeply into the tissues and heal by virtue of the hyperemia produced. A quartz Hg lamp did not cause refractory wounds to heal, while a C arc approximated sunlight in its effects. Rasero, however, reports good results following quartz lamp irradiation of various chronic ulcerations and torpid wounds which had proven refractory to other methods of treatment. Reyn found that the quartz Hg lamp aggravated x-ray ulcerations, atrophy and other forms of injury which healed under the concentrated radiation from a Finsen lamp, the skin becoming smooth and elastic, although the lesions had proven rebellious to all other treatment.

Leo and Vaucher exposed wounds to the sun and made a microscopic study of small pieces of muscle and granulation tissue before and after irradiation. The sun caused a drainage of blood and lymph to the surface, with tissue infiltration and distention of capillaries with red

and polynuclear white cells. As a result of the vasodilatation and surface edema there was an abundant outflow of serum with high antitryptic power, resulting in destruction of bacteria, deodorization and rapid healing. Phagocytosis was apparently not influenced.

Torraca (1921) at the Mosso Institute (2901 M) studied the relative effects of sunlight, shade and bandaging on artificially inflicted wounds of guinea pigs. The best results were obtained with the animals whose wounds were bandaged and kept in sunlight, while the wounds that were freely exposed to sunlight healed more quickly than those kept in the shade. The wounds were aseptic so that the influence was not bactericidal. In a later paper (1922) he reported that quinine and methylene blue accelerated healing in diffuse light and (1924 a) that healing was faster in pigmented than in white areas. He (1924 b) histologically demonstrated that a more copious blood supply was the cause of the more rapid healing.

EFFECTS ON THE EYE. These are of great interest from a pathological point of view since inflammation and injury to the conjunctiva, cornea and lens, as well as to the retina, may take place when the eye is exposed to strong radiation from arc lamps, molten glass, light reflected from snow fields, etc., unless protective glasses are used. Crookes, Coblentz and Gibson and their co-workers, give information regarding glasses for protecting the eyes from injurious radiations.

Penetration. Glancy sees the Sn line 317.5 mμ provided the source is intense enough and Graham reports a subject who claims to see the mercury doublet at 313.2 and 312.6 mμ. Observations on the eyes of cows, pigs, sheep and man show that the shortest wave lengths transmitted by the various portions of the eye are for the cornea 298, aqueous humor 257, lens 313 and vitreous humor (pig) 226.5 mμ, while the combined tissues of the eye absorb the ultra violet up to the neighborhood of 313.4 mμ, the lens being the deciding factor. Saidman and Dufestel claim that it is possible to see as far as 365 mμ. These results may be due to fluorescence of eye-media. Schanz (1922 a) concludes that in an aphakic eye long waved ultra violet is not only visible but can be made to form white when mixed with its complementary. It seems to me that there is reason for believing that the wave lengths in this case are in what one ordinarily calls the visible violet.

A number of investigators have reported that certain lower animals "see" ultra violet rays. Lubbock demonstrated the apparent visibility of ultra violet to ants in 1879. Van Herwerden showed that Daphnia saw ultra violet rays shorter than 334 mμ. Von Frisch claims that the

sensitivity of bees extends as far as 300 mμ, and Lutz believes that bees, wasps and fruit flies see ultra violet as a strong light. Richtmyer, however, is very skeptical of the ability of insects to see ultra violet, because of 25 flowers studied only 4 reflected more than 10 per cent of radiation shorter than 380 mμ. Schiemenz and Wolff believe that fish (Ellritzen) see the 365 and the 340 mμ lines of the quartz Hg lamp respectively.

Aschkinass reported that the transmission, radiometrically determined, of the cornea, aqueous humor, lens and vitreous humor for red and infra red was the same as that of like thicknesses of water, and the total absorption of the eye was equivalent to that of 2.28 cms. of water, the average distance from cornea to retina according to Helmholtz. Radiation longer than 1.4 μ does not penetrate the human eye, but at the limit of the visible spectrum the absorption is not very great. Hartridge and Hill confirmed Aschkinass with more sensitive instruments. The iris obstructs the heat radiation of every wave length which falls upon it, absorbing the same percentage radiation as that which reaches the anterior surface of the lens, roughly 75 per cent of the radiation between 1.3 μ and the visible. The lens, on the other hand, absorbs only about 12 per cent of the energy incident upon it through the pupil. Four times the amount of energy is absorbed per unit area by the iris as by the lens and much more so per unit volume.

Shoji has made a very careful and extensive spectrographic study of the absorption of the various ocular media. Absorption is greatest in the lens, next in the cornea, then in the vitreous and least in the aqueous, but varies in degree in different animals and individuals. For determining the absorption of the entire eye, a minute window was made in the posterior pole of the eye and a small plate of quartz placed therein. The cornea was projected toward the arc, the posterior pole toward the spectrograph.

The absorption of the cornea was studied in man and in monkey and in 11 different kinds of animals. The cut off in the dog is at 306 mμ, in the guinea pig at 293 mμ and in man at 294 mμ. Briefly the cornea may be said to absorb everything shorter than 300 mμ.

The cut off of the lens of the horse is at 372 mμ, that of the owl at 304 mμ. The absorption of the human lens increases with age, the protein content increasing both relatively and absolutely, that of a 65 year old man absorbing everything shorter than 419 mμ, while that of a child of 4 cuts off at 306 mμ. The average wave length at which absorption begins is about 366 mμ. The absorption of the nucleus is

greater than that of the cortex, because of its greater protein content and because the absorption of albuminoids and of beta-crystallin, in which the nucleus is richer than the cortex, is greater than that of the alpha-crystallin which is abundant in the cortex. The absorption of the lens nucleus markedly increases with age due again to its increased protein content. The capsule shows practically no absorption.

In considerable thickness absorption in the aqueous humor is tolerably strong. In a thickness of 7.5 mm., the depth of the anterior chamber of the ox, the cut off is at about 288 mμ, in 10 mm. thickness it is at 305 mμ. The absorption of the vitreous humor also varies according to thickness. For example, that of the horse 10 mm. thick absorbs everything shorter than 305 mμ. In the ox in the thickness that it occurs in life, 22 mm., everything under 295 mμ is absorbed.

The absorption of the eye media as a whole is greater than the absorption of the lens, contrary to the view of Graham. In the horse the cut off for the entire eye is at 375 mμ, for the lens at 368–372 mμ; in the ox 370 and 339 mμ respectively; in the pig 352 and 315, in the rabbit 374 and 352. The absorption of the retina is practically zero, while that of the lens and other eye media is chiefly due to the proteins, of which they principally consist.

In man wave lengths from about 760 to 390 mμ penetrate to the retina and are perceived as light. The cornea transmits to between 295 and 300 mμ, the crystalline lens to between 419 and 306 mμ according to age, with average cut off at 336 mμ, and the vitreous humor to about 230 mμ with a broad absorption band extending from 250 to 280 mμ.

Verhoeff and Bell point out that although the absorption of energy from low temperature sources, like C incandescent lamps and ordinary flames, rises to nearly 90 per cent and is still further increased by reflection, etc., it is quite otherwise with the sun. From such a source the specific absorption of water cuts off relatively little and the total loss of energy in the eye is of the order of magnitude of 25 to 30 per cent. In phenomena like eclipse blindness not only is the eye exposed to a very powerful radiating source, but the radiation is of such character that it is not strongly absorbed and hence the energy in the image must rise to very great intensity.

Injurious effects. Although wave lengths from 295–380 mμ are absorbed by the lens they produce no ill effects as a rule. Ultra violet of wave lengths less than 295 mμ produces severe conjunctivitis and, if long enough continued, corneal ulcers. Sunlight is ordinarily harmless but when increased, as in reflection from large areas of water or of

snow, it produces inflammation and blindness. Artificial illuminants which emit a large amount of radiation of wave lengths less than 295 mμ, such as the quartz Hg and C arcs, etc., are extremely injurious and the eyes should be carefully protected. The inflammation produced by ultra violet is different from that caused by exposure to high powered radiation of no specific wave length, as the light of a short circuit of an electric system or an explosion. The effects of high power radiation, power burn, appear immediately after exposure, the major portion of the energy giving rise to it being in the infra red. The general symptoms consist of temporary blindness, severe eye pain and redness, increasing in severity for a few hours and then subsiding. In the case of ultra violet burns the onset of the symptoms is from 6 to 18 hours after exposure with severe deep seated pains in the eyes. The external inflammation is moderate or absent, and vision is not, but accommodation is, temporarily affected. The eye pain and the headaches may last for weeks, reading and other close work may lead to blurring, the attempt to accommodate to severe eye pain and headache, while an abnormal sensitiveness to ultra violet radiation may persist indefinitely (Sheard).

Verhoeff and Bell undertook to determine the quantitative relations between the amount of energy incident on the eye and the pathological effects. To ascertain whether the effects of powerful solar radiation in producing snow blindness and allied troubles, and the severe scotoma due to direct observation of the sun called eclipse blindness, were proportional to the incident energy they studied ophthalmia electrica, or photophthalmia, in rabbits following exposure to a quartz Hg lamp. The intensity of the lamp is given in ergs per sq. cm., as well as the ergs per sq. cm. as to wave length and the minimal exposure at the stated distance was determined. With a magnetite arc they demonstrated that the limit of abiotic action for corneal cells is about 305 mμ and that the critical amount of radiation shorter than 305 mμ required to set up marked photophthalmia is approximately 2×10^6 erg-sec. per sq. cm.

An ordinary clinical case of photophthalmia, as observed after exposure to arc lights, short circuits, etc., commonly takes the following course. After a latent period of some hours, varying somewhat with the severity of the exposure, conjunctivitis sets in accompanied by erythema of the surrounding skin of face and eyelids. There is sensation of foreign body irritation, more or less photophobia and lacrimation. There is almost always, but unconnected with the photophthalmia

proper, persistent after images, occasional scotoma, erythema and xanthopsia. The least effect that occurs after exposure to abiotic radiation consists in slight conjunctival hyperemia. After more intense irradiation the congestion is correspondingly greater and is associated with edema and purulent exudation. There also may be conjunctival ecchymoses. The cornea, after exposures sufficient to produce slight conjunctivitis, remains clear and shows only slight stippling of the surface. After larger exposures the cornea becomes hazy in a rather sharply defined central area, the epithelium showing marked stippling and being cast off in 24 hours. The haziness usually reaches its maximum in about 48 hours when there is some leucocytic infiltration. After 3 days the purulent conjunctival discharge becomes less, but may not entirely subside for 9 days. The corneal epithelium is usually reformed on about the 4th day. The haziness of the cornea noticeably begins to subside in 3 to 10 days and in 5 weeks only a slight central haze remains. Following sufficiently intense exposures, new vessels are seen extending into the cornea from the limbus in about six days. The greater effects of increased dosage are also described, as well as the histology of the breakdown and repair.

The iris is directly affected only after exposure sufficient to injure the lens epithelium. The clinical changes in the iris are contraction of the pupil, congestion and minute interstitial hemorrhages, with an insignificant exudation of pus cells from the iris vessels. On microscopical examination the lens capsule proper is found unaltered, while the capsular epithelium shows swelling of the cells, appearance of granules in the cytoplasm and the formation of a peripheral wall consisting of a ring of deeply staining closely packed cells at the periphery of the exposed area, that is, in the position corresponding to the pupillary margin at the time of the exposure.

It might be supposed that if a source is not sufficiently rich in abiotic rays to damage the cornea, the retina could not be injured. But if the retinal image is less than that of the pupil the intensity per unit area as concerns transmissible rays will be greater in the retina than on the cornea. Therefore, if the transmissible rays are capable of injuring tissue cells, the macula might be damaged although the cornea and lens remain unaffected. This is what happens in eclipse blindness, due to the heat generated in the pigment epithelium coagulating the retina. Experiments on monkey's eyes and one human eye, as well as aphakic rabbit eyes, showed that it was impossible to injure the retina with abiotic rays.

Snow blindness is a photophthalmia of relatively mild degree and occurs usually only after long exposures and either at very high altitudes or very low temperature or with both these conditions concurring. On snow fields the exposure of the eye to solar radiation, ordinarily greatly ameliorated by the obliquity of the incidence, is rendered much more severe by reflection. Verhoeff and Bell estimate that the radiation reaching the eye under such circumstances is of the order of magnitude of a million ergs per sq. cm. per sec. They see no reason to suspect any specific effects with respect to wave length in regard to possible action of infra red, and regard them purely as a question of heating.

Cataract. Axenfeld regards old age cataract as a natural occurrence found in nearly all persons over 60 years of age to a greater or less extent. Glass blower's cataract occurs often at about the 40th year and begins as a circular cloudiness at the posterior pole of the lens. In time this spreads to the anterior pole and completely fills that portion of the lens exposed to the radiation from the ovens, the part uncovered by the iris, the periphery remaining completely clear.

Following experiments on irradiating frogs and gold fish immersed in 0.2 per cent sodium silicate and in 0.8 per cent calcium chloride with a quartz Hg lamp, Burge assumes that glass blower's cataract is due to the modification by short wave lengths of the lens proteins so that when there is a disturbed nutrition resulting in an increase in salts of calcium, etc., these combine with and precipitate the modified proteins.

Hartridge and Hill suggested a plausible hypothesis of the formation of cataract based on physiological changes in the secretory mechanism of the aqueous. Aqueous is normally secreted in small amounts all the time. When heat falls on the iris a larger secretion occurs, followed, when the stimulus stops, by a period of rest. This stimulus falling regularly for long periods causes the secretory mechanism to be more and more dependent on it. The secretion becomes periodic in character and instead of the lens receiving nourishment all the time, it only receives it at intervals with the result that the least well-nourished part of the eye suffers and develops cataract.

Van der Hoeve regards ultra violet as the principal factor in the origin of senile cataract. By dispersion of a part of the rays against the epithelium of the ciliary processes the nutrition of the lens is interfered with and opacity results.

Schanz (1910) believed that glass worker's cataract is the result of continued illumination, the infra red and luminous rays supporting the action of the ultra violet. Old age cataract, usually beginning in

the lower half of the lens and on the nasal side, is the result of disturbed lens nutrition, due to the day after day action of short waved energy reaching the lower pole in much greater quantities than the upper.

Verhoeff and Bell deny the existence of any sound evidence for the view that senile cataract is due to exposure of the lens to daylight, particularly that from the sky. They incline to the view that glass blower's cataract is secondarily due to the loss of water in the brain produced by the heat on the front of the eye and elsewhere (Leber) and that malnutrition due to interference with the functions of the ciliary body by the heat may be chargeable with the malady (Parsons).

There are two rather divergent and apparently conflicting ideas as to the influence of radiant energy as a causative element in the production of cataract. Both of them may be found to be compatible, for either the infra red or the ultra violet may superinduce cataract under certain physiologic conditions of which we are as yet quite in the dark. It is this knowledge of the physiologic conditions and of the physiologic reactions that energy of various wave lengths produces which we in a large measure lack (Sheard).

Eye therapy. Duke-Elder reports success following local and general use of ultra violet rays in treating numerous eye conditions, tubercular and inflammatory, involving the conjunctiva, cornea, iris, ciliary body, choroid and retina. Mayer and Dworski found that the ultra violet of a quartz Hg lamp, general and local, definitely influences the healing of corneal tuberculosis. Nicolas has used sunlight in treating conjunctival tuberculosis and Passow quartz Hg lamp radiation in cases of eye scrofula and tuberculous conditions in the outer eye. Schanz (1922 b) obtained marked improvement with the quartz Hg lamp in lupus. He also used the C arc lamp with a uviol glass filter in cases of lid eczema, tuberculous iritis and scrofulous conditions. Wright recommends treating trachoma and corneal ulcers by exposure to concentrated sunlight, or, when sunlight is not available, the concentrated light of an electric bulb.

Effects on the circulatory system. There is a general belief that irradiation produces a greater or less drop in blood pressure. Hasselbalch and Jacobaus described decreases in blood pressure averaging between 8 and 10 per cent and lasting for several months following massive irradiation with a large C arc lamp. Cutaneous hyperemia was believed to be the cause and this was considered to afford relief to the heart and large vessels. They cite 4 cases of angina pectoris treated with massive C arc irradiations the results of which are taken

to indicate the use of radiation as a therapeutic agent in this condition. The pulse rate was sometimes slightly accelerated during the erythema. Bach made 109 observations of blood pressure, pulse rate and body temperature after general body irradiation with a quartz Hg lamp on 19 men and 10 women. The blood pressure fell in 105 of them an average of 7.2 mm., the greatest being 17 mm. The pulse became more regular and fuller, but did not change in rate, and there was no change in body temperature. Austgen studied the influence of quartz Hg lamp irradiation on a number of pulmonary tuberculids. Out of 70 cases, the pulse rate was not affected in 11, was increased in 29 and lowered in 30. The pulse usually became fuller and stronger. Loewenhardt found that quartz Hg lamp irradiation produces in tuberculous children a definite and continuous drop of several millimeters (28 and more), the pressure remaining down for a short time after several days of raying, and LoGrasso and Balderrey report a slight drop in blood pressure (119/75 to 113/68) of several cases of pulmonary tuberculosis treated with solar radiation.

Menzer did not find that irradiation produces depression of blood pressure and of body temperature, and Aschenheim and Meyer obtained only a slight drop at the beginning of irradiation, see also Meyer. Rosselet (Rollier p. 211), however, has always observed a fall in blood pressure during insolation, with a maximal increase in pulse rate of between 30 and 40.

Kestner, Kimmerle and Peemöller believe that the depression in blood pressure produced by burning C arc lamps is due, not to the direct action of radiation, but to the inhalation of nitrous oxide given off by the arc. This material, under certain conditions, is also found in the atmosphere even when the sun is not shining. On sultry days, when the barometer is falling and there is later a thunderstorm, the blood pressure of many men drops. The blood pressure of 7 subjects was determined during June and July 1914, in the course of which time there were 4 sultry days, on which the systolic pressure was depressed between 10 and 20 mm. Hg, due to the breathing of nitrous oxide brought downward in the air currents. The Scirocco and Föhn winds, famous for their production of sultriness, are falling winds. Knipping shows that on a trip from Antwerp to the Dutch East Indies the systolic blood pressure drops in different individuals between 10 and 30 mm., but in a month after arrival is up again to the normal. He also regards chemical substances in the air as responsible. Fleming found that blood pressure is not affected by length of stay in the tropics.

The systolic pressure in Manila averages 10 mm. lower than the normal for temperate climates for Americans and 5 mm. lower than normal for the Filipinos. The lowered pressure is due to decreased peripheral resistance. Fleming believes that all objective evidence indicates that whatever effect tropical light may have must be attributed to its thermal action. Roddis and Cooper attribute the depression (10 to 15 mm. Hg) occurring in the tropics to lowered vasomotor tone and a general physiologic slowing down.

Koenigsfeld in 92 observations on 5 persons exposed to a quartz Hg lamp observed a lowering of some 2 to 8 mm. immediately after irradiation and lasting more or less permanently. The cutaneous hyperemia is not the cause of the depression since it does not last as long as the depression. The pulse after irradiation was found to be slower, fuller and stronger, a reaction ascribed to the rest during irradiation. For example: the pulse at the beginning was 76 per minute, after an hour's irradiation it was 68, though lowest after 45 minutes. An hour's rest lowered the pulse rate to 67, the lowest figure reached in 30 minutes being 60 per minute.

Reed obtained marked depression in the blood pressure and heart rate of dogs anesthetized with ether or chloretone, when their atropinized eyes were illuminated with a 500 watt mazda lamp or a C arc. Double vagotomy did not influence the effect while section of the optic nerve decreased it by half. The effect of light on the blood as it flows through the retinal capillaries is regarded as the cause of the depression, similar effects being obtained when the mucosa of the mouth and pharynx, or the blood as it flowed through a quartz tube of 2 or 3 mm. bore interposed in the carotid or femoral artery, was irradiated.

The depression in blood pressure is not the result of cutaneous hyperemia according to Rothman, because it is possible to obtain a drop in pressure without it and no drop in pressure when there is marked hyperemia. It is also not dependent upon the inhalation of gases set free from the lamp. The depression as he has observed it, sets in gradually and lasts for several days. The pressure begins to rise, while irradiation is being continued, at the time the skin begins to be pigmented, and the rise is more or less rapid, according as to whether pigmentation is slow or fast. When pigmentation reaches a certain constant value the blood pressure does also, with a value but little lower than that existing before irradiation.

Rose found that irradiating dogs for an hour per day for 8 days with a C arc (55.44 g. cal. per sq. cm.) lowers the systolic blood pressure by

an average of 13 mm. in 3 to 4 days after the first irradiation and lasting for several days after the last one. The diastolic pressure was not affected as indicated by the instrument used (Kolls). The pulse was temporarily accelerated (6 to 12 per minute) during the irradiation periods. Laurens and Mayerson have continued these experiments. A maximum decrease of between 5 and 20 per cent (average 16 per cent) in systolic pressure and of 10 per cent in diastolic pressure, occurs after the 5th exposure and recurs following subsequent exposures, the usual values being regained, except in a few cases, within 24 hours after each exposure. Long lasting depression was obtained in three experiments on white, short-haired animals, in one a decrease of 20 per cent and 15 per cent in systolic and diastolic pressures respectively and lasting for 3 days after irradiation was stopped. In the others depressions of about 15 per cent in both systolic and diastolic remained for a week and reached normal on the twentieth day after the irradiations were stopped. The pulse rate usually increased an average of 20 per cent during irradiation, but returned to normal soon after. Body temperature usually increased during the irradiation by not more than a degree, and soon returned to normal. The drop in pressure is not due to the action of inhaled substances.

Loewy calls attention to an antagonistic action between high altitude and increased radiation. The blood pressure first rises with altitude, for instance at Davos (1600 M.) the pressure may be increased by 30 mm., the increase being the first response of the vasomotor center to a slightly lowered O_2 content. Above 2500 M. the pressure shows a tendency to fall again due to increased solar radiation.

Exposure to sunlight in the plains increases the pulse by between 1 and 10 beats per minute (Lenkei). Lindhard reports an increase in minute volume and in output per beat, but with a decreasing coefficient of utilization following irradiation. Hasselbalch and Lindhard in an analysis of the effects of altitude and increased ultra violet content on respiration and circulation assert that ultra violet has no marked effect on pulse frequency, though it may slightly retard it. Durig, von Schrötter and Zuntz describe an increase in pulse frequency following intense illumination.

Campbell, Eidinow and Hill bring evidence to show that vasodilatation and capillary stasis in the frog's tongue and mesentery of frog and mouse is due to the ultra violet of Hg and C arc lamps. The higher the temperature, between 6° and 36°C., the more rapidly is stasis produced, but the presence of visible or of infra red rays in great intensity

does not interfere with the action of the ultra violet. Harris regards the widespread peripheral vasodilatation following irradiation of a localized skin area as a nervous reflex (axon and distance) initiated by a noxious stimulus and the whole phenomenon one of incipient injury. Lewis and Zotterman point out that the reaction of cutaneous vessels to tissue injury such as freezing and burning is very similar to that of ultra violet, consisting in local dilatation, reflex dilatation and increased permeability. The underlying cause of these reactions is the liberation of substances having histamine-like action, which diffuse out into the surrounding skin and are conducted away by lymphatic channels. The vessels become dilated because they lose their contractile power.

The long lasting influence on vessels that have been strongly irradiated is shown by the observations of Finsen. On rubbing his arm some six months later the parts that had been irradiated stood out much redder than the other parts. See also Hasselbalch and Jacobaus.

Gassul and Levy marshal considerable evidence in favor of their view that ultra violet radiation has considerably more penetrating power than is usually accorded it. Gassul irradiated white mice with a quartz Hg lamp for varying periods of time up to 18 hours and then killed them. Upon examination a marked hyperemia of the spleen, liver and kidney was demonstrated. In the liver there was marked vasodilatation, extravasation and numerous cases of cell infiltration around the dilated vessels along with scattered clumps of dead cells. Irradiation with red light produced no demonstrable changes in the spleen, liver and kidney. This is regarded as proof of direct deep action on the part of the quartz Hg lamp on the internal organs and blood vessels. Levy irradiated mice and rats for 2 hours at a time for a total of between 14 and 56 hours. The spleen became some 2 to 3 times the normal size, owing to hyperemia of the pulp. There was considerable extravasation as well as disturbance of the follicles with the deposition of large masses of hyaline tissue containing few nuclei, with many heaped up megakaryocytes and much brown pigment (iron). Hyperemia of the liver was sometimes so marked that internal bleeding into the parenchyma took place with considerable cell infiltration and necrosis in the liver tissue. The intensive hyperemia of the lungs often resulted in blood bursting through into the alveoli. Hyperemia in the kidneys was particularly around the tubules. The bone marrow showed a slight hyperemia. Levy believes that these changes must be due to a direct influence on the part of ultra violet on the internal organs, but Clark asserts that it illustrates a distant or indirect action by

means of a reflex or by the transport of a photochemical product, while Hase explains it on the basis of collateral hyperemia.

EFFECTS ON THE BLOOD. Many of the observatons during and following irradiation have been made under the most varied conditions, at high altitude, in the tropics, at sea level, inland and on the shore, with the sun, the quartz Hg lamp and the C arc, on the well, the sick, on children and on adults. There is no wonder that the most diverse results have been described.

Jesionek (p. 355) believes that the pale anemic appearance of those working and living in poorly lighted rooms does not necessarily indicate a change in blood constitution, because it is not the Hb content or the absolute number of the reds which is decreased by lack of light, but the volume of blood going to the periphery. Light, within physiological limits, dilates the cutaneous vessels and thereby allows more blood to go to the skin. It is possible that during a lasting deprivation of light the skin vessels may become constricted and the skin thus assume a bloodless appearance, but such anemic looking people often have a surprisingly high Hb content. Blood studies made during the long winter polar night show that in spite of the pale, yellow-green color of the men there is no change in the blood. Gyllenkreutz found no diminution in Hb in the members of the Spitzbergen expedition, and Blessing reports that the members of the Nansen expedition showed no blood changes as long as the food was sufficient. Bernhard (p. 32) on the other hand is convinced of the harmful effects of the lack of light on man, as exemplified in the anemic condition of those in the Alps who live on the shady side of the deep valleys as contrasted with those who dwell where they are reached by the sun's rays. He believes that the reason why Blessing found no change in the blood of the members of the Nansen expedition is the fact that the winter was spent in an illuminated ship, and that Schoenenberger's failure to find evidences of anemia in mine horses was due to the mines being artificially illuminated. But Grober and Sempell who studied mules that had been kept in very dimly lit, almost always dark, mines between 5 and 10 years found but a slight increase in reds and a corresponding decrease in Hb. The increase in reds is referred to the very good, abundant diet and the hard work that the animals do, an increased metabolism, thus representing an over-compensation against any possible deleterious influence that the lack of sunlight might have.

Miles and Laurens studied the physical characters of the blood of dogs kept for varying lengths of time in total darkness and then returned

to ordinary room light. The factors most particularly studied were reds, percentage Hb, whites and platelets. Isolated observations were made on fragility, coagulation time, total solids and pH. A general review of the literature may be summed up in the statement that irradiation is followed by an increase in reds, whites, platelets and hemoglobin, and a decrease in H ion concentration, coagulation time and eventually in blood volume. In general, darkness causes the reverse, except that blood volume seems also to be diminished in darkness. The outstanding features in dogs of a short period of darkness (15 to 28 days) are: initial decrease in reds with return to normal during the dark period, on readmission of light continuation of normal values with, in certain cases, fluctuating values above and below the normal before a steady level is reached and maintained; initial decrease in Hb with gradual return to normal, on readmission of light no immediate change but a subsequent slight decrease; a transient increase in whites disappearing usually before the end of the dark period, on readmission of light small fluctuations before attaining the usual level. The differential shows evidence of slight changes varying with individual dogs, some showing an increase, others a decrease in polymorphs. Platelets behave similarly to reds, the return to light causing a temporary increase. Total solids are low, indicating blood dilution, coagulation time is slightly increased and a slight increase in H ion concentration of the blood is indicated.

Two dogs were kept for 9 months in darkness. After the usual initial decrease there was a steady increase in reds for about 3 months with lowered counts at the end of 8 months. On readmission of light at this time the reds further decreased before returning to normal. There was indication of a slightly increased fragility of the red cells. The Hb, after an initial decrease, rose with the reds. At the end of 8 months it was lowered and a continued decrease, as with the reds, occurred at the beginning of the light period. The whites, subsequent to the rise occurring at first, showed steadily decreasing values until the time when acute illness, apparently caused by darkness, was accompanied by a marked increase. The number of polymorphs increased in one dog and the platelets were definitely lowered by darkness. Coagulation time was somewhat increased. Just before the end of the 9 months in darkness one of the dogs showed signs of not being well, and light was therefore admitted to the room. The platelets soon increased and the reds decreased, both being effects of exposure to radiation. This was followed by a gradual increase in reds. The percentage Hb

diminished with the reds and later rose to normal. The whites increased sharply then, fluctuating, tended to decrease. Coagulation time was slightly increased.

Levy found that in mice, made anemic by injecting pyrodin, the reds regenerated much more rapidly in animals irradiated with a quartz Hg lamp than in non-irradiated controls. Laquer and Weber showed that artificially made anemic dogs regenerated their blood more rapidly at high altitude than at sea-level. Kestner claims that the effective portion of a high altitude climate is not the reduced O_2 pressure but the increased solar radiation, acting through the breathing of nitrous oxide set free by the action of the sun's rays on the atmosphere of higher altitudes, which getting into the blood stimulates the blood forming organs. Hausmann (p. 105), however, admits no causative relation between increased illumination and the changes in the blood picture which take place at high altitudes. He quotes observations on rabbits made by C. F. Meyer at Davos and Basel which go to show that the increase in reds and in Hb continues when the influence of the sun is excluded although the maximum number of reds was reached more slowly in the animals kept in darkness than in those kept in the light. Knipping studied the influence of sunlight on artificially made anemic dogs on a trip from Antwerp to Borneo and found that regeneration in the tropics was more rapid than in the temperate zones even when the animals were protected from direct irradiation, which prompts him to agree with Kestner that it is the inhalation of chemical substances set free by the action of the increased sunlight which is instrumental. Knipping refutes the more or less generally held view that the paleness of Europeans in the tropics is the result of anemia, this being due to the lack of stimulation by cold, wind, rain, etc. Eijkman comparing the European and the Malay in the Dutch East Indies, concludes that a physiological anemia has not been proven, and Sundstroem regards tropical anemia as a myth. Clark thinks that in the tropics the thermal action of radiation may be responsible for the blood changes observed, namely, high red count, low color index, high percentage of lymphocytes and low percentage of polynuclears.

Burchardi compared the blood of 12 patients irradiated almost daily for 2 to 3 months with a C arc with the blood of 83 patients not irradiated. The increase in Hb and reds was very small, 79.5 to 83.4 per cent and 5,343,000 to 5,978,000 respectively, being more rapid at the beginning and becoming less so as pigmentation proceeded, and finally ceasing after pigmentation became pronounced. A decrease in leuco-

cytes, total and differential, goes along with the increase in reds and Hb, the decrease being due to loss of neutrophiles, the mononuclears and eosinophiles definitely increasing. Häberlin, Kestner, Lehmann, Wilbrand and Georges in a study on a number of children of the benefits to be derived from a stay at the sea-shore found a marked dependence between Hb content and duration of sunshine.

Cramer, Drew and Mottram claim that in rats kept in darkness and in those on a vitamin A free diet the platelets are abnormally few with sometimes a slight anemia which exposure to the quartz Hg lamp soon remedies. Laurens and Sooy followed the blood cell number of the growing albino rat for the first 6 months. They found that the platelets decrease proportionally from a high count in rats exposed daily to sunlight (863,000), to a slightly lower one in rats exposed to diffuse daylight or kept in ordinary room light (747,000 and 762,000 respectively) to the lowest of all (568,000) in rats kept in darkness. The reds similarly decreased, and to a greater extent, so that the platelet-red cell ratio at 6 months of age is greater in rats kept in darkness (1:11) than in those exposed to sunlight or to diffuse daylight (1:13). There was no constant change in total white counts occasioned by darkness, but the polymorphs increased at the expense of the lymphocytes. Irradiation with a C arc gives results similar to those following daily exposure to sunlight. Sooy and Moise report definite beneficial results following the treatment of idiopathic purpura hemorrhagica by exposure to the quartz Hg lamp, platelets and reds increasing, bleeding and retraction time decreasing. Gunn irradiated 6 young rabbits with a quartz Hg lamp and demonstrated a definite increase in platelets, the peak occurring between the 3rd and the 6th days, from which they drop rapidly back to normal. The reds showed a progressive decrease during the first few days of irradiation. In 3 of the animals a level of over a million higher than the original count was attained in 2 weeks and continued for some time after the last irradiation. The leucocytes were not affected. Sanford found that ultra violet irradiation lowers the bleeding time of newborn infants but has no effect on the coagulation time. The platelets are increased, but only temporarily so.

Aschenheim and Meyer studied 16 children during and following solar and quartz Hg lamp irradiation. The children varied in age from 8 months to 13 years and were afflicted with tuberculosis, rickets, anemia or myocarditis, or were entirely well. A single intensive exposure had about the same effect as continued irradiation. All of the children showed changes, some marked, some slight, in the composition

of the blood, there being an activation of most of the blood constituents which continued for some time after the irradiation was discontinued. Sunlight and quartz Hg lamp were practically equally effective. The outstanding change in the majority of cases consisted in an increase in the large mononuclears at the expense of the polymorphs. The total number of white cells did not always parallel the rise and fall of the lymphocytes and leucocytes. The Hb content and the number of reds rose markedly in all cases and remained high, particularly when the value had previously been low. Bernhard (p. 136) reports the results in 5 cases of leucemia exposed to sunlight for from 50 to 100 sun hours. The leucocytosis was markedly reduced, the excessive weakness relieved and the loss of appetite, etc., improved, but of course only temporarily.

Taylor made a series of blood counts in the spring of the year on several individuals who expected to summer at Woods Hole, Mass. In the fall a second series of counts was made on the blood of 38 of these persons who showed more or less evidence of tanning. These was no constant change in the total whites. The neutrophiles tended to vary in inverse proportion with the lymphocytes. The tanning was accompanied in 25 of the 38 individuals by an appreciable increase, percentage (27.27 per cent) and absolute, in the number of circulating lymphocytes. In 8 there was a definite decrease (15.2 per cent) and in 5 there was no appreciable change.

Baumann found in men, following massive doses of quartz Hg lamp radiation, at first an inconstant, rapidly disappearing and slight increase in lymphocytes, followed by a relative and absolute increase in lymphocytes which repeated irradiation further increased along with the eosinophiles and large mononuclears. The changes in guinea pigs were more striking, one increase from 8,800 to 16,400 being recorded. Following massive doses the differential shifted so that in 6 to 8 hours the polymorphs represented 75 per cent of the total with a corresponding decrease in lymphocytes. The mononuclears were sometimes increased by 20 per cent and nucleated reds were sometimes found.

Clark points out that the white blood cells, as contrasted with the reds, respond to short exposures of any radiation, and that all the published results agree in the conclusion that ultra violet radiation stimulates a lymphocytosis in man and animals. Rabbits were exposed to an iron arc so that only the ears, from which the hair had been clipped, were irradiated. In addition to the naked arc screens were used with the following results: Wave lengths shorter than 300 to 330

mμ produced a marked lymphocytosis, but had no influence on the polymorphs. Wave lengths between 330 and 390 mμ decreased the number of lymphocytes with no action on the polymorphs. Wave lengths from 450 to 650 mμ stimulated the formation of lymphocytes and to a slightly less extent the polymorphs. Wave lengths longer than 650 mμ had no influence on the whites except the characteristic drop which follows immediately after irradiation of any kind. Blood counts made on Americans in the Philippines and on native Filipinos show an increase in the percentage of lymphocytes and a decrease in polynuclears. Koopman irradiated 5 well and 3 ill persons (pulmonary tuberculosis, chronic nephritis and diabetes). The number of reds remained unchanged, the whites increased during the first hour and then decreased, remaining low for 6 hours. The neutrophiles increased during the first 3 hours, after which they decreased. The lymphocytes steadily increased, while Hb, viscosity and coagulation time remained unchanged. The normal amboceptors showed decreased effect, but there was never any variation in the resistance of the red cells to hypotonic salt solution.

LoGrasso and Balderrey report increases in Hb in cases of pulmonary tuberculosis following solar irradiation, 42 out of 49 cases showing an average increase of 10 per cent, and only 4 remaining stationary. In practically all there was an initial leucocytosis with the polymorphs predominating, both being decreased following treatment, with relative increase in lymphocytes. Balderrey and Ewald treated 15 cases of tuberculosis for more than 3 months with C arc radiation and found that the Hb was increased by 67 per cent, the reds by 50 per cent, the lymphocytes by 50 per cent and the leucocytes by 17 per cent.

Bickel and Tasawa irradiated brown and white rabbits for from 1 to 8 weeks daily with a strong quartz Hg lamp. The brown rabbits showed an increase in reds and Hb, but the white did not. The increase in Hb content after 1 week was 5 per cent, after $5\frac{1}{2}$ to 8 weeks, 15 per cent. The reds after $1\frac{1}{2}$ weeks' irradiation were increased by 480,000, after 8 weeks by 3,400,000, plainly indicative of new formation, as evidenced by an increased number of megakaryocytes in the bone marrow, and a large number of reds and a smaller number of whites in the spleen as compared with the counts for normal animals.

Riedel treated some 48 cases of surgical tuberculosis and rickets with combined solar and quartz Hg lamp radiation. The Hb was definitely increased, as much as 34 per cent in the very anemic cases. The improvement is ascribed to sunlight. The red cells also increased and

strikingly so in 70 per cent of the cases. In many, quartz Hg lamp irradiation succeeding solar treatment was followed by an actual decrease in Hb and in reds, and alone produced but a slight increase. The increase in reds at high altitude is not merely due to the lowered O_2 pressure, but to the increased intensity of solar radiation. Not only was the amount of Hb and the number of reds increased, but the color index as well. Riedel found no typical action of sunlight on the whites though radiation with the quartz Hg lamp produced a decrease in 55 per cent of the cases, an increase in 30 per cent, and no effect in the remainder.

Koenigsfeld in 92 observations on irradiation with the quartz Hg lamp reports no influence on reds and Hb. Even 4 minute irradiations, however, produced an increase in whites, with return to normal in 3 to 4 days. Fifty to sixty minute irradiations produced sustained increases. After one irradiation a relative increase in polynuclears and often of large mononuclears takes place. After several there is a sudden decrease in polynuclears with a slow drop in the large mononuclears while the lymphocytes increase. There is a simultaneous eosinophilia, occasionally as great as 14 per cent. Still longer irradiations cause another increase in polynuclears with a decrease in lymphocytes with but slight evidence of eosinophilia. The changes in the white counts soon disappear. The leucocytosis is comparable to a digestive leucocytosis with no new formation but simply a greater call owing to an increased metabolism.

Hobert studied the action of darkness, of room light and of quartz Hg lamp irradiation on the regeneration of red cells in mice that had been bled so that the number of reds was reduced to about half the normal. In such mice kept in darkness the reds and Hb increased gradually and attained a maximum about $\frac{1}{3}$ lower than the normal in between 18 and 22 days. Immediately after bleeding there was a leucocytosis, an increase from between 11,000 and 14,000 to between 43,000 and 57,000 from which high count there was a rapid fall to a figure somewhat above the normal. In animals kept in daylight the regeneration is quicker, the reds increasing more rapidly than the Hb, the determinations on the 13th and 14th days showing values somewhat higher than the average. The leucocytes increase to between 26,000 and 28,000 returning to normal at about the same time that the reds do. Normal, as well as anemic, mice were irradiated. In normal, unshaven mice irradiated with a quartz Hg lamp for 2 minutes the reds quickly increased by some ten times. In 6 hours the count

was normal. The leucocytes likewise increased and then gradually decreased. Successive irradiations for longer periods with 3 day pauses in between likewise produced definite but smaller increases in reds, in Hb and in whites, particularly the polynuclears.

The irradiation of the anemic animals was started at a minute, repeated every 12 to 14 hours, with increases of 2 to 4 minutes until the 5th to the 7th day. The Hb and reds increased regularly until the single irradiations lasted 16 minutes, when the values commenced to decrease, falling lower than those at the beginning of the irradiation. The animals were listless and showed loss of appetite. Since it seemed as if the irradiations might be given too frequently, 3, 4 and 5 day intervals between successive doses were instituted, the duration of the irradiations being gradually increased to 30 minutes. In between 9 to 10 days the original value of reds and Hb was reached and passed, the Hb increasing the more rapidly. Nucleated red cells in varying numbers were present throughout and an eosinophilia of between 17 and 22 per cent. Other anemic animals were irradiated for 4, 10, 20 and 30 minutes with 5 day pauses between. In 10 to 11 days the original values for Hb and reds were attained, Hb again increasing more rapidly with many nucleated reds. Among the whites the polynuclears again showed the greatest percentage gain. Of considerable interest is the demonstration that too much, or too frequent, irradiation is definitely harmful. Hobert regards the damage as of double nature, first in the too rapid maturing of the reds (as indicated by the greater increase in Hb followed by the formation of more reds), succeeded by an accelerated storing of reds, giving rise eventually to an anemia.

Miles and Laurens studied the influence of known amounts of C arc radiation on dogs. In moderate dosages there was an initial increase in reds, followed by a decrease; with double this dose there was an immediate decrease. Following the irradiation the reds increased by 1,500,000 above the former normal figures. This is taken to indicate a stimulation of the blood forming organs, obscured at first by increased blood volume. There is further a decreased percentage of total solids, further indication of initial blood dilution, as well as decreased Hb, both values reaching normal shortly after the irradiation period. In two abnormal dogs, one recovering from long confinement in darkness, the other showing loss of weight, probably occasioned by a previous strong irradiation, an increased percentage Hb was obtained which quickly dropped to normal in the post-irradiation period. The whites showed marked fluctuations above the normal level, but diminished

following the irradiation and the number finally returned to normal. In dogs given a strong dosage the normal is not maintained, the count dropping to a still lower level. The differential shows lymphoblasts and myelocytes, increasing lymphocyte or large mononuclear percentages and many smudges. After irradiation there is indication of an increase in polymorphs at the expense of the lymphocytes but with early return to the normal percentages. With the moderate dosage the platelets increased, while with the stronger dosage they decreased, followed in the post-irradiation period by definite increases above normal. Mayerson has recently published a continuation of this work. Three white, short-haired dogs were exposed daily, or at short intervals, to moderate or massive doses of measured C arc radiation. A primary increase of about 30 per cent in blood volume, evident during the first exposure, is accompanied on successive exposures by an increase of about 10 per cent in red cell number and volume and Hb. The increase in reds is maintained in two experiments, in one animal for six weeks after the last exposure. The red cells in the post-irradiation period are smaller in size and, except in one experiment, of normal saturation. Two animals showed a post-irradiation rise in platelets. Leucocytes in all experiments show a maximum post-irradiation decrease of about 50 per cent.

Albela discovered no difference between the opsonic content against Staphylococcus pyogenes albus in irradiated (quartz Hg lamp) and non-irradiated rabbits and guinea pigs. Sonne reports that by virtue of the action of the luminous rays in heating the blood to above fever temperatures (47 to 48°C. in and below the skin) toxins may be destroyed. White guinea-pigs subcutaneously injected with minimal lethal doses of diphtheria toxin and then treated with the visible rays from a 50 amp. C arc for 2 hours endure the toxin much better than non-rayed animals do. He claims that something more than 40 per cent of the injected toxin is destroyed by the light bath. Hansen found that massive doses of C arc radiation influenced the agglutinin in human blood following the injection of typhoid vaccine. The amount is increased and its disappearance from the blood retarded. Irradiated rabbits withstood much better the injection of killed typhoid bacilli than did non-irradiated. The explanation he offers is that of Sonne. Koenigsfeld found that the formation of hemolysin, agglutinin and precipitin, but not of complement, was enhanced by irradiation, while Koopman reports that the activity of serum complement of guinea pigs irradiated for one hour was almost doubled, while 6 hours later it

was normal. Irradiation of from 2 to 3 hours markedly diminishes it, while an irradiation of 3 hours kills the animals, there being no complement found at death. Irradiation in vitro of guinea-pig serum for 3 hours inactivates complement. Colebrook reports observations which go to show that exposure of a normal subject and one who is in poor health but without any obvious infection may have opposite effects on the bactericidal power of the blood. A normal man thus developed a quite exceptional high power two hours after a sun bath and maintained it for several hours. Another subject whose bactericidal power was considerably below the normal level before the sun bath went from bad to worse and the blood had not regained its normal level 24 hours later. The changes were entirely referable to changes in the function of the whites, since the bactericidal power of the serum was not influenced. The fall in bactericidal efficiency stands in agreement with the well attested clinical observation that patients suffering from severe infections—such as active pulmonary tuberculosis, may be made worse by exposure to sunlight. Both the serum and the leucocytes contribute to the increased bactericidal effect achieved by the blood of rabbits after they have been exposed to various radiations (C arc, Hg lamp, Alpine sun in the winter, invisible heat) or to blistering agents which produce inflammation of the skin. The increase in hemobactericidal power is found also in pigs and to a less degree in man (Colebrook, Eidinow and Hill).

Sonne's view that the local heating of the blood by irradiation increases the specific antibodies of the body is not true (Hill). Hartley finds that light baths have not the least effect on specific immunity, although they do increase the general resistance of the body to infection by increasing the bactericidal power of the blood. If irradiated blood is injected into an animal from which it has been withdrawn the bactericidal power of the blood is increased although this power has been actually destroyed in the irradiated blood itself, as are the ferments, serum agglutinins and anaphylactic power.

Considerable work has been done on hemolysis by ultra violet. Hausmann demonstrated that in ultra violet hemolysis decomposition of the Hb was not related to it and that O_2 was not necessary to it, at any rate in the medium surrounding the cells. Hausmann and Loewy showed that normal rabbit red cells diluted in salt solution to 1 to 500 and 1 to 1000 are hemolyzed by the sunlight at Davos during the later part of February and the beginning of March. Even skylight there has a weak hemolytic action, though it requires several hours of action.

Both sunlight and skylight are still very weakly active after passing through glass.

Koeppe has studied the hemolysis of red cells by in vitro and in vivo irradiation with the quartz Hg lamp. He reports that the effective wave lengths in vitro are shorter than 270 mμ and the effect increases with decreasing wave length. The hemolysis is due to injury to the cell membrane thus setting free Hb by an oxidative decomposition, dependent upon catalase, of the fatty constituents. The blood of different children shows slight but clear differences in resistance to the hemolytic action of in vitro irradiation. A series of irradiations in vivo renders the corpuscles more resistant to later irradiation, though during one irradiation the red cells are actually damaged as they are in vitro. The resistance continues to increase slightly for a few days after the irradiations and then decreases again. The increased resistance is due to the acceleration of the disappearance of the less resistant and the increase in the more resistant corpuscles. The mode of action in vivo is assumed to be similar to that demonstrated in vitro, but it hardly seems possible, in the light of our present knowledge, that the in vivo action can be to any very great extent dependent upon wave lengths shorter than 270 mμ.

Effects on metabolism. *General metabolism.* Although there is a general belief that sunlight is beneficial observation has suggested the possibility that men and animals can live in darkness for a relatively long period of time without serious functional disturbance. The statement that light increases metabolism is insufficiently supported by experimental data.

Graffenberger concluded that the chief effect of partial darkness on the metabolism of rabbits is a lowering of C metabolism leading to the formation and deposition of more fat. Oltramare found that many animals (rabbits, guinea pigs, chickens, pigeons, tortoises, frogs, salamanders and fish) could live in darkness as long as three months without showing any outstanding untoward effects. Two phenomena are considered to take place, an augmentation of reserves and a diminution in exchange. The animals in darkness increased in weight more rapidly than those in light, although receiving the same amount of food, and there was a correspondingly greater increase in the glycogen reserve.

Mayerson, Gunther and Laurens found that subjecting normal adult dogs on an adequate diet to short periods (18 to 28 days) of darkness acts as an initial stimulus to metabolism which usually decreases to normal by the end of the dark period. This is evidenced by an increase

in total acidity, an increased urinary nitrogen and chloride excretion and a marked rise in blood P. The Ca and P balances indicate a retention. On readmittance of light there is a similar increase in metabolism which persists for a short time. The rise in urine and blood N is accounted for in large measure by increase in urea, suggesting an increase in endogenous N metabolism by the exclusion and readmission of light, supported by observed rises in creatinine, phosphates and chlorides. There were no marked changes in the constituents of blood and urine during the stay in the dark, merely during the transition periods. In order to see whether a longer stay would produce effects dogs were kept in darkness from February 25 until November 11. The chemical composition of the urine and blood was not materially altered after the initial changes subsided, although the resistance of the animals seemed to be lowered.

Further observations on dogs showed that deprivation of light for short periods results in a gradual rise in urinary N to a peak in about 5 days, with decrease in the N balance, soon recovered from so that at the termination of the dark period (18 days) the balance is normal. On readmittance of light there is a characteristic sharp rise in both urine and feces N resulting in a marked decrease to a negative balance, which soon becomes normal. In one case there was a slight N retention, increased positive balance, which markedly decreased upon reexposure to light. All but one of the animals increased in weight (0.5 to 1.5 K.). There is an initial drop in Ca accompanied by a rise in P, a secondary rise in Ca and a simultaneous drop in P and this in turn is followed by a rise in P and a drop in Ca both constituents being at lower levels at the end of the dark period. On return to roomlight P rises and then quickly decreases while Ca rises. Both constituents then decrease to levels lower than at the beginning of the experiment. The balanced relationship is very marked.

Mayerson, Gunther and Laurens also give the results of a study of the effects of irradiation of dogs with the C arc. The question was whether radiant energy, being such a powerful stimulus to pathological and deficient metabolism, would influence an already positive "normal" metabolism. The total energy of the lamp used was 0.924 g. cal. per sq. cm. per min., (0.0154 g. cal. per sq. cm. per sec.), which is to be compared with the average seasonal solar radiation intensity at sea level (Washington, D. C.) of between 1 and 1.2 g. cal. per sq. cm. per min. (0.0155 g. cal. per sq. cm. per sec.). The energy distribution, however, is quite different, for the lamp being approximately: 22 per

cent ultra violet, 43 per cent visible and 35 per cent infra red, while we may take solar radiation at sea level as distributed as follows: between 1 and 2 per cent ultra violet; 42 to 53 per cent visible, and 57 to 63 per cent infra red.

The irradiation of normal adult dogs with moderate intensities (55.44 g. cal. per sq. cm.) increases endogenous N metabolism, stimulates the absorption of Ca and P from the intestine and usually decreases the amount of blood sugar. The changes persist and in some cases are most apparent in the post-irradiation period. A repetition of the exposure of 1 hour for 8 days after an interval of 20 days gives results similar to those obtained when the single exposures are lengthened to 2 hours for 8 days. Serum P is markedly increased by irradiation (arc lamp and roomlight following darkness) in some cases as much as 300 per cent. On moderate exposures to arc lamp radiation there is a balance between the serum Ca and P. Excessive (110 g. cal. per sq. cm.) or repeated irradiation also increases serum Ca, the rise coming simultaneously with that of P.

The observations demonstrated an unexpected similarity between the effects of change from roomlight to darkness and vice versa and the effects following irradiation. There is in both a stimulation of endogenous N metabolism resulting in a decrease in the balance and the changes in the partition of Ca and P in urine and feces resulting in P retention are present in both. We might expect that the transition from darkness to roomlight would produce results somewhat similar to irradiation with a strong source of radiant energy, but it is somewhat surprising to find that a change from light to darkness shows similar, if less pronounced, effects. Probably any deviation from the usual, in so far as radiant energy is concerned, acts as a stimulus which disturbs the metabolism of these constituents. The results are similar to those of Crofts and Laurens on the influence of light upon respiration in the frog, in which the absence of light disturbs the equilibrium in the same way as does a short exposure to radiation. Long continued darkness allows the animal to adjust the equilibrium but on return to roomlight it is again disturbed. Intense dosages similarly disturb the equilibrium to such an extent that recovery requires a longer period of adjustment. These experiments are indicative of a relationship between a positive or negative variation in the amount of radiant energy acting upon the organism and an initial disturbance in metabolism.

Mayerson finds that when the abdomen, instead of the back, is irradiated with a moderate dose both serum Ca and P decrease markedly,

though a second abdominal irradiation period results similarly to dorsal irradiation. Blood samples drawn after individual exposures give lower values than those taken before, the decrease disappearing by the next morning. This is ascribed to an increased blood volume due to vasodilatation and diffusion of water from the tissues as a result of the irradiation. The decrease in both Ca and P observed in the first abdominal irradiation period is explained as a lasting dilution, with no recovery between successive exposures, due to the much more severe and extreme vasodilatation under these conditions.

Koenigsfeld reports that irradiation of men with the quartz Hg lamp increases protein metabolism, N elimination increasing markedly and changing from a positive to a negative balance, the increased N excretion being followed by a compensatory N retention. The chloride, sulphate and phosphate elimination is increased and there is an early decrease in weight and an increase in appetite, comparable to that produced by muscular exercise. On the other hand, the relation between extra-renal and renal secretion is changed similarly to the way that it is by body rest while high altitude influences metabolism similarly to radiation with the quartz Hg lamp.

Wiener carried out two long metabolic experiments on normal men, irradiating them with a C arc (the "ultra sun") having no ultra violet shorter than 290 mμ. During irradiation N excretion was decreased, while after it there was a shift to a N equilibrium on a higher level than that holding during the preliminary period, and the negative balance became positive. S excretion was not affected, that of P was decreased, indicating retention, and there was an increase in uric acid and purine base excretion of about 80 per cent on the first and third days of irradiation with return to normal. After an interval of 6 days, renewed irradiation called forth a similar increase in uric acid excretion. Eichelberger reports that creatinine excretion is increased during an hour of irradiation (C arc or sunlight), then decreased for several hours, after which it returns to the preliminary level. Heat is shown not to be the causative factor. Pincussen (1924) showed that insolation at an altitude of 1500 M increased the breakdown of protein and of nuclein compounds, considerable oxalic acid arising from the decomposition of xanthin, guanin and uric acid.

According to Pincussen (1922) C arc radiation increases the reducing power of glucose solutions, while in serum irradiated in vitro the sugar diminishes more rapidly than it does in darkness. In whole blood there is an increase in reduction, apparently dependent upon substances in

the corpuscles set free by hemolysis. In vivo experiments on white rabbits irradiated with strong electric glow lamps indicate that irradiation does not influence the glycolytic ferment, but leads to a decrease in blood sugar. When the animal is sensitized with eosin and other dyes there is at first a decrease followed by an increase in sugar. The results are construed as being due to two processes, first, an increased sugar mobilization, and second, an increased oxidation. Pincussen also found that irradiated rabbits had a higher blood sugar after adrenalin injection than those not irradiated, pointing to an influence of radiation on the sympathetic. Irradiation following the injection of eosin leads to a reduction; following injection of adrenalin to an increase; and following injection of both to an increase in blood sugar but a smaller one, further evidence of increased mobilization and destruction of sugar. Diabetics were irradiated with a quartz Hg lamp or with a strong glow lamp. Following the injection of eosin a strong irradiation led in one patient to a decrease in blood sugar, the urine sugar being reduced to zero in about 13 days. In another, irradiation with the quartz Hg lamp resulted in marked improvement with decreased sugar in the urine as well as decrease in acetone. Several cases proved refractory. Dejust suggests that Pincussen obtained an increase in reducing power of glucose solutions when irradiated with ultra violet on account of evaporation.

Bloch and Faber found that while the fasting blood sugar of a number of non-diabetic children was not affected by quartz Hg lamp irradiation, that of 2 diabetic children was reduced by as much as by 3 or 4 units of insulin, rising the day after to the original value. The decrease is assumed to be due to increased oxidation caused by an increased excretion of insulin by the pancreas.

Rothman, believing that he had demonstrated that irradiation produces a decrease in sympathetic tone (hypo-adrenalemia), investigated with Callenberg the question as to whether this was bound up with a shift in K and Ca concentration between the skin and blood. A single general irradiation producing a marked skin inflammation increases serum Ca very considerably the day after irradiation, for example, from 9.2 to 13.2 mgm. per cent, accompanied by marked inflammation; 5 days later the serum Ca is 9.8 mgm. per cent, the inflammation having disappeared and practically all the pigment. If a single massive irradiation results in pigmentation the serum Ca remains above the original level. For example, before irradiation the serum Ca was 9.75, the day after a 20 minute exposure it was 11.4 mgm. per cent with marked in-

flammation and rose-red skin. Seven days later the serum Ca was 10.3 mgm. per cent, the skin a brownish-red. If irradiation is repeated, resulting in a second dermatitis, Ca again rises, but if pigmentation is marked then a repeated irradiation does not further increase serum Ca. The rise and fall of Ca during the development and disappearance of inflammation reflects the degree of sympathetic tone. This decreases during inflammation, increases gradually with incipient pigmentation and continues to do so as pigmentation increases. Blood Ca remains high during continued irradiation even though the treatment is continued for some weeks, and the lasting increase in Ca corresponds to the lasting sympathetic hypotonia which is present when pigmentation is complete.

Barkus and Balderrey found that the exposure of full-grown fasting sheep to sunlight and the radiation of the quartz Hg lamp hastened the disappearance from the blood stream of intravenously introduced phosphates and sulphates, and the exposure to the C arc caused a high concentration ratio relative to intravenously introduced hypertonic phosphate solutions independently of body temperature and water and chlorine diuresis. They conclude that the observed decrease in plasma P is due to dilution resulting from diffusion of water from the tissues rather than to increased elimination.

Clark, assuming that ionized Ca is bound electrically by the negatively charged proteins, and considering that ultra violet radiation by discharging these proteins should free some of the bound Ca, thus increasing the percentage of ionized Ca, irradiated serum in quartz test tubes with the quartz Hg lamp. She found that the percentage of diffusible Ca was always increased unless it was very high to begin with, which may account for the action of ultra violet on Ca metabolism, since it is the ionized, not the total, Ca which is of importance in maintaining the Ca to P ratio.

Hart, Steenbock and Elvehjem present evidence that irradiation with the quartz Hg lamp influences the storage of Ca and P and the equilibrium of these elements in the blood stream of mature animals in a way similar to the effects upon growing animals. Two lactating goats and a dry goat were brought into distinctly negative Ca balances. Upon daily irradiation with a quartz Hg lamp the negative Ca balances were changed to positive, and the inorganic blood phosphorus was appreciably increased. On such levels of Ca and P intake mammary secretion brings on rapidly a negative Ca balance as compared to non-lactating animals. Hart, Steenbock, Elvehjem and Scott also report

on the influence of sunlight and the quartz Hg lamp upon Ca equilibrium in milking cows.

J. B. Orr, Magee and Henderson and Henderson and Magee describe the results of irradiating goats showing negative Ca balances with a C arc. The negative balances were converted into positive, or markedly reduced, concurrently with increased secretion of milk, presumably due to increased absorption of Ca. Henderson studied two pigs kept in semi-darkness on a low Ca and high P ration. Over a period of 10 days the retention of Ca (particularly) and of P showed a decrease. Following this one of the animals was irradiated with a C arc with a definite increase in Ca and P absorption and retention, while the other animal continued to show the decrease in retention accompanied by loss of appetite and gastro-intestinal disturbance. Bone analyses showed that the actual percentages of CaO and P_2O_5 were definitely higher in the irradiated pig although the ration was the same in both. In observations on 3 pigs on a diet well balanced as to Ca and P, one was kept in the diffused light of the room, the other two in semi-darkness, but one of these was irradiated for an hour a day with a C arc. Over a period of 50 days there was little difference in the Ca and P retention of the 3 pigs, what small difference there was being in favor of the irradiated one.

Pincussen and Makrineos observed that in a number of convalescents showing no metabolic disturbances the blood K definitely decreases after 3 or more irradiations with a quartz Hg lamp. The changes in Ca were much smaller, the ratio between the two being sometimes decreased as much as 25 per cent. Pincussen (1925, 1926) also studied the influence of sunlight at the end of March at Davos, Switzerland, on young white rabbits. Irradiation, as in humans, decreases the blood K with no characteristic change in Ca, the ratio between the two being much reduced, owing to an increased excretory ratio. The amount of Ca excreted is also markedly diminished so that following irradiation the ratio of Mg to Ca is markedly decreased. No work was done on blood Mg, but it seems clear that Mg plays an increased rôle in metabolism following irradiation. The amount of K in the liver of the irradiated animals was sometimes twice that of the control dark animals.

Reed and Tweedy found no constant change in the amount of blood Ca of anesthetized and heparinized dogs whose blood as it flowed through a quartz tube in the carotid artery was irradiated by a C arc. Denis and Corley report that daily irradiations with a Hg tungsten arc were without effect on the Ca content of the tissues and serum, and Howe

and Medler found no evidence that the gratifying clinical results following irradiation of tuberculids is connected with an altered metabolism of Ca or P.

Grant and Gates report progressive variations in Ca due apparently to the season and to caging. From a low level of 11.74 in January high levels were reached in May and November of 12.92 and 12.88 mgm. per cent in rabbits received from various dealers. Similar variations were found in rabbits that had been caged for 1 to 7 weeks with the blood Ca at a higher level (13.12 mgm. per cent) and the January at 12.40 and the May and November peaks at 13.62 and 13.47 mgm. respectively. In general, the longer the animals were caged the higher the blood Ca rose, showing an increase from 12.52 to 13.65 mgm. per cent during a period of 7 weeks. Rabbits irradiated with a quartz Hg lamp over corresponding periods of time showed similar increases in blood Ca during the period of progressive parathyroid hypertrophy. Coincident with the subsequent drop in the size of the parathyroid glands there was a drop in Ca to the original level. Blood P determinations showed that in the irradiated rabbits the highest levels of both P and Ca coincided with the period of most marked parathyroid hypertrophy and that both elements in the blood fell during the following period when the glands were undergoing regression. Gates and Grant (1926) fed cod liver oil or irradiated cholesterol to adult male rabbits for periods of several weeks and at autopsy compared the weights of certain of their endocrine organs with those of normal rabbits and of rabbits irradiated with a quartz Hg lamp over similar periods of time. The changes, except in those animals directly irradiated, when the external parathyroids and the hypophysis were hypertrophied, were all within seasonal variations and there was no significant progressive variation from normal levels in the Ca and inorganic P levels of the blood.

These authors (1927) have sought to determine the significance of the parathyroid hypertrophy found in rabbits after exposure to ultra violet radiation. Since it is not accompanied by a corresponding increase in blood Ca the upper level of this would seem to be governed by factors independent of parathyroid control and the hypertrophy under the influence of ultra violet may represent a potential functional capacity, or increased factor of safety, to protect the Ca level under conditions of stress or emergency. Partial parathyroidectomy in irradiated rabbits, compared with the same operation in normal controls, results in a similar immediate drop in blood Ca; but there is a more rapid

restoration of the Ca level in the irradiated animals, indicating a more prompt and active response to the emergency on the part of the remaining glands. No significant differences were found in the reactions of irradiated, normal or partially parathyroidectomized rabbits to injection of $CaCl_2$ or disodium hydrogen phosphate. All 3 groups rapidly eliminated the excess Ca from the blood, while their reactions to large subcutaneous doses of sodium phosphate appeared to be related to phosphate elimination or retention in the individual animal. No distinctions could further be drawn between normal, irradiated and partially parathyroidectomized fasting rabbits. Blood Ca was reduced similarly in all three groups and the serum P showed such wide individual variations that no deductions could be made. However, the irradiated animals suffered disproportionate losses of weight during the fasting and 4 of 5 died, their deaths being attributed to more rapid consumption of their own tissues and possibly also to suprarenal injury caused both by the fasting and the exposure to ultra violet. Nonidez and Goodale found that the combined effect on the parathyroids of chickens deprived of ultra violet shorter than 312 mμ and on a ration poor in antirachitic vitamin is enlargement of the glands, due to hypertrophy and hyperplasia, followed by regression.

Pearce and van Allen (1926) demonstrated a relationship between the season of the year and the general character of disease, in that the actual hours of sunshine, together with the rate, extent and persistence of change in the curve of sunshine could be related to the character of experimental disease. The experiments were carried out in rooms in which the sunlight was filtered through glass so that the effects cannot be attributed solely to the so-called therapeutic ultra violet rays. These observations led the authors to the conception of a relationship between the nature or character of light and the physical state and functional activities of the animal. They give the results of an investigation with controlled conditions of light on the normal rabbit with special reference to organ weights. The light room was illuminated by 1000 watt Mazda lamps and glass Hg lamps, there being no wave lengths shorter than 310 mμ. The control animal room had a southern exposure lighted by two windows. Groups of normal male rabbits were kept under conditions of constant light and constant darkness respectively for 2 to 12 weeks. The general health of the rabbits was not impaired by the light nor by the exclusion of it, though the gain in weight was particularly in those kept under conditions of constant illumination.

With the environment of constant illumination two principal effects upon organ weights were observed. First, a definite tendency toward smaller relative weights, particularly striking in the case of the liver, kidneys, gastro-intestinal mass, thyroid, parathyroids, hypophysis, pineal, spleen and lymph nodes. In the case of the liver, the thyroid and the parathyroids this tendency could be noted when the organs of rabbits living under ordinary indoor conditions were large or were increasing in weight. The thymus appeared to be an exception to this general effect of diminished organ weights. The second effect was a stabilization of organ weights in contrast with the more pronounced irregularities or fluctuations observed in the control groups. The majority of the organs of rabbits kept in constant darkness also showed a tendency toward decreased and stabilized weights, but less pronounced than in those in constant light. The weight of the liver was, however, markedly increased. The results support the conception that there is a relationship between light and the physical state of the animal organism as expressed by the trend or direction of organ weight.

Pearce and van Allen (1927) also report an experiment in which an environment of constant and continuous light and one of constant darkness have influenced the course and character of a malignant disease of rabbits induced by a transplantable neoplasm. Under the influence of constant light the level of malignancy was low, while under the influence of constant darkness it was somewhat lower than in the control animals living under ordinary indoor light conditions, but not as low as among the animals constantly illuminated. The observations furnish experimental evidence in support of the idea that there is a correlation between the external factor of light on the one hand and the manifestations of an experimental malignant disease on the other. In earlier work it had been found that, in general, the periods of maximum and minimum sunlight corresponding with summer and winter were associated with relatively low levels of malignancy while the periods of greatest malignancy occurred at times of abrupt and rapid changes in the hours of sunshine, coinciding roughly with the spring and autumn months. Pearce and Brown found that under the influence of constant light the level of malignancy was lower than in control animals living under ordinary conditions of diffused sunlight, while under the influence of constant darkness the level of malignancy was somewhat lower than in control animals.

Brown and Pearce refer to earlier work which indicated a relation between the course of infection of experimental syphilis in rabbits and

prevailing meteorological conditions (hours of sunshine over a given period of time) and a tendency to a seasonal periodicity with maximum severity at some time during the spring and fall, and report the results of a series of experiments carried out for the purpose of determining whether the reaction of rabbits inoculated with Treponema pallidum might be influenced by their light environment. The conditions were diffuse sunlight filtered through window glass, constant and continuous exposure to the radiation of glass Hg arcs, and darkness. In general the efficiency of the reaction to infection increased with the amount of light received and with the constancy of the exposure, and it is evident that changing conditions of light environment are a disturbing factor and may counterbalance the beneficial effects of the light itself.

Pincussen demonstrated that certain protein splitting ferments and nucleases found in the blood following irradiation of the entire body are derived from destroyed body cells and white blood corpuscles. With Coelho he irradiated white rabbits with a quartz Hg lamp and found 30 minutes later that while the nuclease blood content was definitely increased, that of the ester splitting ferments was not.

Some mention should be made of the action on the nervous system with particular reference to psychic influences, since sunlight is unquestionably one of the various factors having to do with the sensations of bodily and mental well-being. Striking results have also been reported following irradiation with Hg and C arc lamps. Even after a dose so mild that it does not produce erythema there is a feeling of exhilaration expressing itself in the joy of work and of living, Hausmann feeling as if he had been on a mountain trip. Hasselbalch describes his sensations following a two hour irradiation with a strong C arc producing a marked erythema. Instead of the usual evening fatigue with frequent yawning he felt lively and indefatigable. The feeling of exhilaration and of desire and ability to work usually lasted two days, the "light mania" being followed by deeper depression than usual. Hasselbalch suggests that "light mania" may be a kind of immunity against depression. The action on the nervous system is evidently indirect and depends upon improvement in circulatory and metabolic conditions.

The effects of an overdose of radiation, well known and personally familiar to most of us, are accompanied by feelings of unrest, more or less vague apprehensiveness, sleeplessness, etc. In many these symptoms appear long before the erythema.

Rickets. It is now established that there are 4 factors, Ca, P,

vitamin and radiation, the lack of any one of which plays an important part in the production of rickets. The exposure to radiation or the administration of cod liver oil stimulates the deposition of inorganic salts and particularly affects the P and Ca metabolism of the body. According to Park, rickets is a disturbance in the metabolism of the growing organism of such a nature that the salt equilibrium, in particular as regards the Ca and P, in the circulatory fluids is disturbed, and lime salts no longer deposit in the bones. Lime salts may not deposit because the ionized Ca in the blood is low or because the ionized P is low, or because both are low. However, when Ca is low the formation of new bone and the destruction of old calcified bone are greatly accelerated, and the pathological process takes on a distinctive character.

William Huntly in 1889 stated that sunlight was the thing to counterbalance the evil of the filth and diet surrounding the natives of Rajputana and in 1890 T. A. Palm wrote that sunlight was the cure for rickets. Raczynski chemically examined the bodies of two puppies of the same litter nursed by their mother. One puppy had been kept in the sunlight, the other confined in the dark for 6 weeks. The body of the first contained much more Ca and phosphate than did that of the second, and Raczynski concluded that the lack of sunlight is one of the causes of rickets. Huldschinsky showed that rickets was cured by irradiation with the quartz Hg lamp and with sunlight, and Hess and Unger demonstrated that sunlight alone possesses the curative action exercised by the energy radiated from the quartz mercury lamp in human rickets. This was taken as indicating that hygienic factors, and not dietetic, play the dominant rôle in the marked seasonal variations of the disorder. Hess, Unger and Pappenheimer then found that rachitic lesions which develop regularly in rats upon a diet adequate in Ca but low in P may be prevented by short exposures to direct sunlight and that this protection is equivalent to the addition of at least 75 mgm. of P to the diet in the form of basic potassium phosphate. The same authors compared the action of sunlight with that of C arc and Hg arc radiation. Young rats on a diet low in P and high in Ca or low in Ca and high in P were found to be protected from rickets by insolation for 15 minutes daily, though in winter this degree of irradiation was insufficient, and the effective rays of sunlight do not penetrate window glass. Irradiation for 3 minutes at a distance of 3 feet from a quartz Hg lamp prevented rickets, as well as 2 to 3 minutes at 3 feet or 1 hour at 6 feet from a C arc lamp. Pigmentation was regarded as lessening the effect of radiation as demonstrated by the failure of a standard dose

of irradiation to protect black rats from rickets. Kramer, Casparis and Howland, and Kramer and Boone found, however, that the pigment of the skin of the negro child did not interfere with the action of radiation.

Hess and Weinstock using screens with various cut-offs in the ultra violet demonstrated that in order to be of value against rickets ultra violet rays must have a wave length not longer than 302 mμ or possibly 313 mμ. Luce reports that a screen with a cut off at 296 mμ and a 0.5 per cent transmission at 305 mμ absorbs the effective wave lengths of sunlight preventing rickets. Screens respectively transmitting to 240 mμ, and with 80 per cent transmission at 300 mμ, and transmitting wave lengths 265 to 425, with a 77 per cent transmission at 300 mμ, both transmit wave lengths in sunlight which are protective against rickets. Tisdall and Brown studied the variations in the ultra violet content of the antirachitic effect of the sun's rays throughout the year. They report that the sun's rays in December in the latitude of the city of Toronto produce a definite antirachitic effect on rats, and December skylight possesses almost as marked antirachitic effect as the available sunlight. December sunlight passing through ordinary glass is not antirachitic, while sunlight passing through Vita-glass, transmitting as short as 262 mμ, is roughly one-fourth as antirachitic as direct sunlight.

The two most important theories as to the etiology of rickets are that it is due to deprivation of daylight or that it is caused by defective diets. Numerous experiments have indicated the importance of the inorganic constitution of diets, in particular of the P, in relation to the disease. Diets deficient in fat-soluble A alone do not produce rickets, the pathological condition induced being osteoporosis. The vitamin A of earlier observers has been separated into two elements. The one is a thermostable substance that is not destroyed by heating cod liver oil at 120°F. for twenty hours in excess of oxygen, and is concerned with the calcification process. It is the true antirachitic factor, or vitamin D. The other is vitamin A proper, thermolabile and destroyed by heat and oxidation, and is concerned with differentiation of cartilage cells to form osteoblasts. A deficiency of this substance leads to osteoporosis, sclerosis and disordered bone growth as well as being associated with the prevention of ophthalmia. The antirachitic factor works not only in the retention of Ca in rickets but also in the adult in which rickets is never observed. It represents specifically the organic agent which promotes normal Ca anabolism. It may cure rickets, it may promote growth, or it may simply prevent excessive loss of lime from the body.

Radiation revives a depressed function. Rats on a diet deficient in

the antirachitic factor grow normally and their bones calcify normally provided they are irradiated 10 minutes daily by, e. g., a quartz Hg lamp, but radiation cannot act as a substitute for the factor, and when it is completely absent from the diet radiation cannot bring about normality in either growth or bone calcification, the degree to which they approach normality depending upon the preëxperimental store of the factor.

Rickets may begin at any time but the highest percentage of early manifestations of the disease is between November and May. Almost all children who are born in the fall and die in the spring show marked manifestations of rickets, in contrast to children born in the spring and dying in the fall who are almost free from it. Hess and Lundagen demonstrated a seasonal variation in the level of the inorganic phosphate of the blood of normal infants which corresponds to and is determined by the seasonal variation in the richness of the solar spectrum in ultra violet rays. The frequency and severity of craniotabes agrees with that of rickets, reaching maximum severity during March and April, and responds to the same therapy. Reisenfeld, Handelman and Rose did not find individual sunlight exposure and the available sunlight in the community to be such obvious causative factors in the inorganic P content of the blood of infants as they had expected from the current literature on rickets, while relative humidity and inorganic P content of the blood of the new born infant show a striking parallelism, the points of resemblance in the former preceding the latter by 2 months. The relation is explained on the basis of an accentuation of the effects of the ultra violet by removing minute particles from the air which act as ray filters. A divergent opinion is voiced by Reyer and Schmaucks who conclude that sunlight plays a subordinate rôle in the improvement noted in summer, the healing being chiefly due to diet. They observed that healing in winter may occur on a purely dietary basis (sufficient vitamin content) without solar or artificial radiation, and that florid rickets may occur in summer when the children are fed a diet either partially or wholly lacking in vegetables.

Mackay and Shaw point out that clinically there are two aspects to the treatment of rickets: the effect on the general health, and the effect on Ca and P metabolism. Although irradiation usually improves both in a rachitic child they cannot be regarded as having an identical pathological basis. As regards the retention of Ca and P, cod liver oil and ultra violet radiation are interchangeable, but the same is not true of the general health. Ultra violet cannot replace all the physiological effects of cod liver oil and similarly cod liver oil

cannot replace radiation in many of its physiological effects. Phototherapy usually brings considerable general improvement in the activity, muscle tone and contentment of rachitic infants whereas cod liver oil has much less general beneficial effect.

Kramer, Casparis and Howland demonstrated that systematic quartz Hg lamp irradiation of children caused healing of rachitic bone processes, increase in serum phosphate (2.9 to 6 mgm.) and calcium deposition in the bones in a way identical with similar results following cod liver oil treatment. In active rickets, unassociated with tetany, there occurs regularly a marked reduction of the concentration of inorganic P in the serum with, in some instances, a moderate reduction of Ca concentration. With active rickets the reduction is such that when the concentration of Ca expressed in milligrams per cent is multiplied by the concentration of P the product does not exceed 30. In healing the product is 40 or above, while normally it hardly ever exceeds the value 66 (Howland and Kramer). Holt defines rickets, not as a state in which the concentrations of Ca and P are so low that $Ca_3(PO_4)_2$ cannot be precipitated, but as a state in which, as a result of lowered ion concentrations, it is deposited so slowly that new bone production exceeds it in rapidity and consequently uncalcified bone or osteoid tissue is produced. The ion product is taken to be a more accurate criterion of the rate of deposition of $Ca_3(PO_4)_2$ and hence of the activity of rickets than is the empirical Ca times P product.

Eckstein observed that irradiating rachitic rats with a quartz Hg lamp shortened their lives, while the non-irradiated, although their development was slow, remained alive in comparatively good condition. He believes that the disturbed metabolism is further strained by the irradiation and that the unfavorable action of the quartz Hg lamp was due to its being a too strong stimulus. He therefore used a C arc lamp, wave lengths shorter than 290 mμ being filtered out, and concludes that ultra violet rays are not specific in their action on rickets, but that metabolism is in some way affected by the general irradiation and that this works indirectly on the diseased organs. The C arc was found to cure and prevent rickets, in dark rats as well as in albinos, but did not seem to lengthen life.

Orr, Holt, Wilkins and Boone construct the picture of the rachitic disturbance as follows: The primary, as yet unexplained, difficulty is a defect in the capacity of the intestine to absorb Ca and P, thus resulting in a low concentration of these elements in the serum and in defective calcification. Cod liver oil and radiation, with no increase in the

intake, act so that the absorption of these elements from the intestine occurs much more readily and their concentration in the serum rises until the deposition of calcium phosphate in the bones becomes possible. Cod liver oil and radiant energy act, not only as regulators of Ca and P metabolism, but also permit the organism to operate with greatly increased economy and efficiency. Maximal utilization of minimal quantities of Ca and P is produced and a reduction in the waste of these elements must be the result of maximal absorption from the intestine. Something is supplied the body which enables it to assimilate and hold bone salts (Park). Grayzel and Miller report experiments which add evidence in favor of the view that the primary defect in rickets is an impairment of absorption and that ultra violet rays (and cod liver oil) affect the degree of absorption of phosphate (and Ca) from the intestine. A rickets producing diet caused a definite rise in the pH of the contents of the intestines even to alkalinity in dogs and ultra violet irradiation (or cod liver oil administration) changed the reaction to the normal range, the gastric contents showing no change (see Telfer).

Hart, Steenbock, Lepkovsky and Halpin demonstrated that the chick requires a liberal supply of the antirachitic vitamin or its equivalent, radiation. On a ration low in the antirachitic factor chicks receiving no sunlight were listless and inactive, rough of feather, awkward in gait, etc., and died within 6 weeks, while a sunlight group were alert and active and with almost natural smooth feathering. Bethke, Kennard and Kik found that a half-hour of direct sunlight promotes growth and is more effective in preventing leg weakness in chicks, by acting as a calcifying agent, than green clover fed at a level of approximately 18 per cent, although the clover prolonged life, increased growth and delayed the onset of leg weakness. Hughes and Titus regard the etiology of leg weakness in chicks and rickets in mammals as the same from the point of view of the blood content in Ca and P and their general pathology, namely, a faulty metabolism of Ca and P, resulting in an improper calcification of the bones, but Pappenheimer and Dunn dissent.

Maynard, Goldberg and Miller report that sunlight increases the assimilation of Ca and prevents the development of leg stiffness in pigs on a ration low in Ca or in the factor favoring its assimilation.

The question as to whether irradiation of the mother produces a protective quality which can be transmitted through the milk to the young or to other animals is one that has received considerable recent attention. Observations by Luce indicated that, while sunlight of

summer intensity in England had no significant effect in raising the growth promoting value of cow's milk when the diet of the cow is deficient in fat soluble vitamins, the degree of exposure appeared to have a small effect in determining the antirachitic value of the milk. According to Chick and Roscoe the vitamin A content of milk depends on the diet, being at a maximum on fresh green food and least on a winter feed of cereals and roots, but it is independent of the degree of exposure of the cow to sunlight. The vitamin D content, on the other hand, depends principally upon the degree of insolation of the cow, promoting growth and preventing rickets in rats on a low P diet. However, the diet contributes something, in that fresh green food seemed to produce milk with the maximum antirachitic value, while that yielded by the cow receiving a diet of cereals and roots, though exposed to maximum sunlight, appeared inferior in this respect. When the cow was out at pasture in summer the milk contained the maximum amount of both A and D.

Hess, Weinstock and Sherman report the production of antirachitic human milk by irradiating the mother. Rickets was induced in rats, after which 25 cc. of human milk was substituted for the rickets producing diet with no beneficial results, the inorganic P remaining very low. The woman was then irradiated for a month with a quartz Hg lamp. The milk then fed to a lot of rachitic rats had very beneficial results, healing taking place with marked calcification of the epiphyses and increased inorganic P. This is of some interest when we realize that rickets occurs in from $\frac{1}{3}$ to $\frac{1}{2}$ of breast-fed infants in the temperate zone.

Gowen finds that the milk of cows irradiated with a quartz Hg lamp is markedly antirachitic as compared with that of non-irradiated. Falkenheim, Voetz and Kirsch, however, report that when a cow on a vitamin-free fodder is irradiated with a quartz Hg lamp the milk has doubtful clinical benefit when administered to rachitic infants, the amount of healing being but slight. Experiments on rats, however, indicate that the milk has acquired strong antirachitic properties, being superior to the milk of cows fed normally. Hart, Steenbock and their associates found that the egg production of hens is greatly influenced by the supply in the diet or environment of the antirachitic factor, even when there is plenty of lime in the ration. The irradiation of hens was also found to greatly improve the hatchability of their eggs as well as the amount of lime in the shell, but the Ca and P content of the whites and yolks was not distinctly increased, nor was the fer-

tility of the eggs consistently influenced. The developing embryo from the eggs of irradiated hens contained, after 21 days of incubation, nearly twice as much lime as those from non-irradiated hens, and the antirachitic potency of egg yolks from irradiated hens was approximately 10 times that of egg yolks from the non-irradiated hens.

Nelson and Steenbock show conclusively that when irradiated and non-irradiated rats are kept in the same cage the stimulation to growth exerted upon the non-irradiated is mediated by their consuming the antirachitically activated excreta of the irradiated animals, only the merest traces being found necessary.

Tetany. Infantile tetany is a condition often complicating rickets, but, although the general character of the relationship to rickets is apparent, the exact nature of the metabolic disturbance necessary for its development is obscure (Park). Tetany is a symptom complex which occurs in rickets when the salt equilibrium in the blood happens to be of a kind which sets the nervous system in a state of hyperexcitability, namely, low Ca, and it is with the low Ca form of rickets that manifest tetany is associated. If tetany can be considered a disease then it is the same deficiency disease as rickets and is cured and prevented by exactly the same means and differs from rickets only in the fact that the salt equilibrium in the blood happens to assume a special form or forms. Tetany, according to Huldschinsky is due to the taking away of Ca from the tissues, while in rickets there is a pathological inability on the part of the bones to bind Ca. Rickets is not influenced by Ca feeding, while tetany can be caused to practically disappear by its administration. Howland and Marriott showed that any agent capable of raising the Ca concentration to a level within 20 per cent of the normal will cure the active manifestations of tetany. Even with cod liver oil and Ca therapy the return of serum Ca to a normal figure may be very slow, although the clinical manifestations may disappear fairly promptly. The demonstration of a low concentration of Ca in the serum is therefore a valuable aid in the diagnosis of infantile tetany and the demonstration of its return to normal is probably the most reliable sign of the cure of the disease.

Sachs cured both latent and manifest tetany by irradiation with the quartz Hg lamp, and Huldschinsky likewise cleared up 6 cases of spasmophilia. Casparis and Kramer irradiated 5 children (1 negro) suffering with active tetany with the quartz Hg lamp, bringing about a subsidence of the manifestations and curing the accompanying rickets. In every instance the Ca concentration of the serum was increased while

the inorganic P was raised to the normal level or above, which is not true following the administration of $CaCl_2$. (See also Hoag.) Woringer believes that infants must have light in order to maintain a normal Ca content, the lack of it being the chief cause of abnormal Ca metabolism.

According to Falkenheim and György, the favorable effect of irradiation on tetany is indirectly through its action on rickets. If the influence of radiation, and of cod liver oil, were limited to Ca ionization the results would be the same as those following treatment with Ca salts, ammonium chloride, etc., which is not the case. It has been frequently shown that definite improvement in tetany does not occur until after a number of irradiations and a short and mild irradiation gives rise to an alkalosis and increased vagotonia. Irradiation with a quartz Hg lamp therefore may lead to more marked manifestations of tetany as long as the rachitic metabolic disturbances exist and a latent tetany become manifest. In uncomplicated rickets irradiation does not usually result in tetany. The period of healing in tetany following treatment with the quartz Hg lamp corresponds exactly with the healing of rickets. During the first days of irradiation the lowered serum Ca does not rise to any extent, the serum P being practically normal. Later the serum Ca markedly rises, while the serum P remains constant or slightly increases, until the usual ratio between Ca and P is attained. The treatment of tetany with radiation requires, the authors think, simultaneous antirachitic measures, the most appropriate being a supply of Ca salts. Huldschinsky holds a similar view.

Swingle and Rhinhold found that while Hg lamp radiation prolonged the life of parathyroidectomized dogs, up to 25 days, ameliorating the violent symptoms, it had no influence on the Ca content of the blood serum. The benefit is believed to be due to improved absorption and retention of Ca. Jones reports that the daily administration of 20 cc. of cod liver oil for 2 weeks before operation prevents tetany and greatly increases the length of life, to an average of 32 days, of thyroparathyroidectomized dogs. Similar results, but not so striking, were obtained by irradiating the dogs. The concentration of the Ca in the blood fell as rapidly as in the treated, and in fact the lowest levels attained were in the blood of the treated dogs which lived the longest. Pinkus, Peterson and Kramer state that irradiation with the quartz Hg lamp does not influence the Ca concentration of the serum in tetany parathyroipriva, though it does so in infantile tetany. They succeeded, however, in keeping dogs alive for 6 to 8 weeks by irradiating them,

the Ca reaching a certain minimal concentration which is maintained for a long time with freedom from convulsive seizures.

Drucker and Faber find no support for the view that the hypocalcemia of tetany is due to an "alkalosis." Quartz Hg lamp irradiation produces a practical saturation of the blood with Ca, but leaves the blood reaction almost unchanged. They call attention to the fact that the antagonistic relation between P and Ca does not occur following irradiation, since they both rise.

Growth. Definite examples of the influence of light on normal development are few and are concerned for the most part with animals who have lived for generations in the light. The literature dealing with the development of frogs, salamanders, fish, insects, hydroid polyps, etc., is reviewed by Hausmann and Jesionek. In a few instances it is clear that light exerts an influence, as in the regeneration of polyps by Eudendrium. The action of radiation on the healing of wounds is in great measure due to influence on cell division. Of particular interest is the development reported by Kammerer of a functional eye in the blind cave salamander Proteus, following appropriate exposure to light. Cave animals are not necessarily animals whose ancestors had normal eyes which through disuse have undergone a gradual hereditary degeneration. Fruit flies kept for 69 generations in darkness show perfect sight and reactions. The blindness of certain cave fish seems to be due to imperfect circulation in the embryonic eye probably owing to some interference with normal development, due to an hereditary defect.

Higgins and Sheard found that exposing frog eggs to the radiation of the quartz Hg lamp accelerated their growth for 24 hours, followed by retardation culminating at the end of the third day with characteristic anomalies of development. Hinrichs reports various abnormalities following the irradiation with a Hg lamp of Fundulus eggs soon after fertilization. A transitory stimulating effect was produced in only a few cases.

Northrop calls attention to the fact that although light is one of the most striking attributes of the environment of living organisms, the results of practically all of the experiments designed to show its effects on the normal growth processes of animals have been negative. He undertook to determine whether or not the rate of growth and total duration of life of Drosophila are affected by variations in the intensity of the light radiated by Mazda lamps. He found that the duration of the larval periods of Drosophila which had been previously grown in

the dark for 200 generations is shortened slightly at intensities around 2500 meter candles, but becomes increasingly longer at higher intensities. The larvae are killed by continuous exposure to light of 7000 to 10,000 and the pupae at intensities greater than 5000 meter candles. Above 1000 meter candles the duration of the imago period is rapidly shortened and a rate of aging is produced which is proportional to the intensity of the light. He obtained no evidence to show that inbreeding, absence of light, or growth in the absence of bacteria for 230 generations has any effect on the duration of life or on the ability of the organism to resist unfavorable bacteria.

Frank studied the growth of 100 healthy well-nourished children up to 2 years of age. He found a sharp rise in the growth curve from April to June, a drop during the hot summer months, a second rise in September to November and a depression in December and January. Average temperature, amount of precipitation and of sunlight could not be correlated. The rapid increase in growth in the spring may be due to the greater vitamin content of the diet, particularly the milk, fed after a vitamin-poor period. The slowing down of growth in the summer seemingly contradicts this view, while the second advance in the fall is hardly so to be explained, since the diet at this time is no richer in vitamin than it is at the height of summer. The results go to show that several factors play a part in regulating growth.

Borissow reported that dogs and rabbits grown in light weighed at the end of a month more than those grown in dim light and concluded that light acts as an excitant for the organism so that tissue change goes on more rapidly, but at the same time nutritive materials are fixed with more facility. Goldblatt and Soames showed that rats on a diet containing an optimal quantity of Ca, P and fat soluble organic factor, grow equally well with normal calcification of their bones whether kept in darkness or in daylight supplemented by radiation from a quartz Hg lamp. Cramer and Drew state that rats kept in a dark room since birth do not show any obvious signs of ill health, growth proceeding at the same rate as in rats kept in well lighted rooms on the same diet. Degkwitz kept puppies in darkness where they were vigorously exercised daily and reared free from metabolic disturbances. Histologically the bones and organs were normal and the dogs weighed more at the end of the experiment than others in light. Examination of the organs and tissues showed a decrease in total ash in darkness; a distinct impoverishment in Ca, P and Mg, and an increase in K, and the skin of about half of the dogs showed increases in P and Na. The

N retention in the dark animals was lower, especially so in the animals fed a protein rich diet. The animals were apparently normal in condition so that the author believes that the process is one of adaptation. In the dark the ash content simulated more or less that of rachitic organisms but histologically the bones were not different from those kept in the light. The lack of light did not make the animals rachitic but increased their tendency to rickets.

Goldblatt and Soames demonstrated that young rats if irradiated with a quartz Hg lamp from the time they are put on a diet very deficient in the fat soluble vitamins, grow more rapidly, reach a higher maximum weight, continue to grow for a longer period and show a better condition than do control rats. Similar differences between irradiated animals and controls were observed in the case of a litter of rats brought up by a mother who was fed on the same deficient diet during the latter part of pregnancy and the early period of lactation. During the first 4 to 5 weeks, despite the deficient diet, the radiated animals grew at practically the normal rate for rats of that age but then slowed up and finally ceased. Rats irradiated when growth has ceased for only a short period and when the entire store of fat soluble vitamins is not completely exhausted, resume growth for a short period, then cease and show a decline in weight and finally death, and rats whose growth has definitely ceased for 2 weeks or longer do not resume growth as a result of irradiation and their subsequent history is unmodified. In some instances decline in weight seems to be accentuated and death hastened. Irradiation with the quartz Hg lamp is thus shown not to be a substitute for the growth promoting factor and synthesis of it does not occur on a diet deficient in it as a result of irradiation, but the economy of its action is improved, so that for continued normal growth the presence of the growth promoting factor is necessary in only small amounts if the animals are daily irradiated. This growth promoting property can be induced in vivo, for if rats are kept on a diet deficient in growth promoting factors until they have ceased gaining weight for about 4 weeks, their livers when fed to other rats do not possess growth promoting properties, but if, after complete cessation of growth, rats are irradiated with a quartz Hg lamp for a few weeks their livers acquire the property of stimulating for a short while the gain in weight of rats that have ceased growing on a diet deficient in the growth promoting factors.

Eckstein found no outstanding difference between the rate of growth of rats irradiated with a quartz Hg lamp and those not so irradiated,

except that if the dose was excessive growth might be slightly inhibited. Animals kept in darkness for several weeks but irradiated show accelerated growth and greater weight than do those not so irradiated, so that improvement takes place when the environment is unfavorable. Rats on a vitamin-free diet remain alive in comparatively good condition although their development is slow. If they are irradiated they die in from 12 to 31 days, the disturbed metabolism not being able to stand the additional strain put upon it by irradiation. Laurens and Sooy studied the growth of albino rats kept constantly in darkness, in ordinary room light, in ordinary room light but given daily exposures of diffuse daylight and of those given daily exposures of direct sunlight. The rate of growth was in the order named. Springer and Tardieu report observations on 5 rabbits born and kept in a dark cellar. The three weakest irradiated with ultra violet grew normally, while the two strongest kept as controls, gradually lost weight, finally developing paralysis and dying. There were no signs of rickets.

Sundstroem (1922) found that the light from Mazda lamps acts as a stimulant to the growth of mice exposed to it for long periods of time at ordinary room temperature, but that the retarding influence of stagnant humid air is added to by exposure to this artificial light. He (1926) found little evidence that tropical sunlight as such had any effect on the growth of rats, the harmful effect of a tropical climate seeming to be in the decrease in cooling power of stagnant air. A series of experiments is described in which one set of rats was continuously fanned while the controls were housed under stagnant air conditions. There was no evidence of improvement in growth, which is slower than in temperate regions, but the weight of the internal organs was appreciably higher in them than in the controls, due, it is thought, to a general rise in the general metabolic level.

Hart, Steenbock, Lepkovsky and Halpin showed that sunlight was of practical importance in the rearing of chicks, acting as a supplement, or the equivalent, to the antirachitic factor, and Bovie demonstrated that wave lengths 300 to 330 mμ are necessary for their normal growth and development. Goodale found that irradiated chicks did not affect non-irradiated when they were penned together and that the eating by non-irradiated chicks of the droppings of irradiated chicks was ineffective in promoting growth. Irradiation for one minute twice weekly at 3 feet from the lamp gave normal growth and less frequent irradiation was inadequate. The natural covering of the chicks is not penetrated by the effective wave lengths and the main receptor is the small amount

of naked skin about the bird's head. Winter sunlight is apparently both growth promoting and preventive of leg weakness, and the effective wave lengths are between 208 and 312 mμ.

Sheard and Higgins report experiments on the germination and growth of seeds which lend support to the view that the near ultra violet rays aid in the growth of cells or of the normal functioning of an organism kept under unphysiological environment. Further that these wave lengths stimulate the endogenous growth of cells and of the organism as a whole while the longer wave lengths influence the exogenous metabolic processes. Coward shows that irradiation with a quartz Hg lamp accelerates the formation of vitamin A in plant tissues (wheat, white and yellow corn), but does not have any influence on the ultimate amounts of the vitamin.

Activation of inert substances. The demonstration that certain substances inert, in so far as antirachitic, bone calcifying and growth promoting powers are concerned, may have these capabilities bestowed upon them by irradiation (Hess, 1924, Steenbock and Black 1924) is of more than usual interest. The fact that skin, liver, lung and muscle, as well as eggs, milk and feces acquire calcifying and growth promoting properties is a matter of scientific and clinical importance. That an animal when irradiated has constituents in its body so activated has far reaching implications in connection with our ideas as to the mode of action of radiation, as has the fact that diets which are deficient in certain respects may be made complete by irradiation or by the addition of irradiated substances such as cholesterol. A list of the substances which have been activated includes the following: olive oil, linseed oil, cottonseed oil, corn oil, nut sterol, cholesterol, phytosterol, skin, dextrin, wheat, wheat flour, milk, milk powder, Steenbock's yellow corn rachitic ration, chicken mash, spinach, lettuce, orange juice and sawdust. Some of the things that have proven refractory to activation are: a solution of chlorophyll, Hb, red blood cells, cream, oleic acid, egg phosphatide, mineral oil, casein and agar.

Hess and Weinstock (1924) demonstrated that cottonseed oil and linseed oil, but not mineral oil, acquired antirachitic property when irradiated, as evidenced on rats fed a rachitic diet. The oils showed a slightly changed unsaturated fatty acid content, the total acidity being somewhat increased, while the color was slightly bleached and they acquired a somewhat fishy odor resembling that of cod liver oil. The irradiated oils stored this factor for a considerable period. Wheat grown in the light and irradiated with the quartz Hg lamp conferred

antirachitic protection when fed to rats as contrasted to wheat grown in the dark. Green lettuce leaves became antirachitic after irradiation, though leaves from the market were of no value in preventing rickets.

Steenbock and Black (1924) and Steenbock and Nelson also reported that rat rations are activated by irradiation with the quartz Hg lamp becoming growth promoting and having calcifying power to the same degree as when the rats are irradiated directly. The activation takes place when the irradiation is done in an open dish, in a stoppered pyrex or quartz flask filled with air or CO_2, but not in a brown glass bottle. The quality is not destroyed by subjecting the ration to a vacuum, heating it for 45 minutes at 96°C. or letting it stand for 24 hours at room temperature. Lung, muscle and liver irradiated after removal from the body by a quartz Hg lamp were activated, becoming growth promoting and bone calcifying. Dutcher, Creighton and Rothrock found that when Steenbock's yellow corn rachitic ration was irradiated by a quartz Hg lamp the inorganic blood P and the percentage of bone ash of rats reared on it was midway between the usual and the value for rachitic rats.

According to Hume and Smith the apparent action of air that has been irradiated with a quartz Hg lamp in preventing rickets in rats is due to the activating action of the radiation on the sawdust that was placed in the bottom of the jars. The beneficial action of the irradiated sawdust on growth and calcification is conferred by the animals eating it, and not by secondary radiation which it may emit. Nelson and Steenbock demonstrated that the antirachitic, growth promoting reaction induced in non-irradiated animals, caged with irradiated, is due to the ingestion of photochemically activated constituents of the excreta, and that irradiated animals do not give off radiations capable of exerting an antirachitic effect upon their neighbors.

Steenbock, Hart, Hoppert and Black report that irradiating cow's milk with a quartz Hg lamp increases its antirachitic activity 8 or more times, goat's milk about 24 times. Kramer treated 8 children suffering from active, severe rickets with a diet of orange juice, cereal and irradiated milk. The level of inorganic P increased in the serum and reached approximately the normal level in 4 weeks and roentgenograms showed well marked or complete healing at the end of the 4th week. In 2 cases in which the Ca and P balance was studied there was a marked increase in the retention of both during the period when the irradiated milk was fed. Dawkins and Pattison gave irradiated milk to 5 children with active bone tuberculosis, who had shown during 4 months' observation

no marked improvement on the hospital diet including cod liver oil and milk, with marked increases in the red cells and Hb.

György found that milk irradiated with a quartz Hg lamp acquired a taste resembling that of cod liver oil (jecorized milk) and cleared up the symptoms of rickets and tetany in 16 out of 18 children to whom it was administered. He also successfully treated 20 cases of rickets with irradiated milk powder, which retains antirachitic properties for at least 4 months. Reyher reports that if milk is irradiated in quartz vessels from which the oxygen is removed the impairment of the odor and taste is partly prevented.

Drummond sounds a warning in regard to the irradiation of milk. Though thus activated it not only becomes unpalatable, acquiring an unpleasant tallowy odor, but suffers the destruction of vitamin A by oxidation, so that if it is the chief part of the food of rachitic children they will receive an inadequate supply of this vitamin. Furthermore, if the irradiated milk is being employed medicinally as an antirachitic it is hard to understand why it should be used in preference to the more potent and not so much more unpalatable cod liver oil. A number of other foodstuffs do not appear to suffer deleterious changes during irradiation. Many vegetable oils contain the precursor of the antirachitic vitamin, but little if any vitamin A, and become antirachitic following irradiation. They are relatively palatable and may be used when cod liver oil is not well tolerated.

Steenbock and Black (1925) present detailed evidence of the antirachitic activation of fats. They discovered that excessive irradiation of cod liver oil and of olive oil inactivates them. Activated olive oil kept in a stoppered bottle in the dark was found unimpaired after 10 months. The antirachitic potency of irradiated fats lies in their non-saponifiable fractions, as in cod liver oil. Mineral oil cannot be activated. Activation may be induced by the radiation of quartz Hg, C and Fe arcs and by sunlight, and the effective wave lengths are not longer than about 300 mμ. Old oils (cocoanut, corn, oleo, peanut and cottonseed), acid in reaction, cannot be activated and the same is true of the non-saponifiable constituents of old oils.

A 1 per cent suspension in water of a pure as possible phytosterol prepared from cottonseed oil was irradiated by Hess, Weinstock and Helman and fed to rats on a low P diet. In contrast to non-irradiated phytosterol, which does not protect against rickets, the irradiated preparation does. Irradiated purified cholesterol from brain tissue gave similar results. Cholesterol is apparently activated by the same wave

lengths, about 300 mμ or less, as those which have been found to be specific in rickets when animals are subjected to direct irradiation (Hess and Weinstock, 1925 b).

Hess and Weinstock (1925 c) find that a chemical change in cholesterol takes place when it is endowed with antirachitic potency by irradiation, absorbing ultra violet to a less degree than does ordinary cholesterol, and the absorption continues to decrease with increasing degrees of irradiation. If, however, the irradiation is prolonged beyond a certain point the cholesterol becomes less transparent than non-irradiated cholesterol. When activated cholesterol is kept, in a watery suspension or in a dry state, its spectral transmission becomes gradually diminished until it transmits less than it did originally. Schlutz and Morse and Schlutz and Ziegler also studied the absorption spectrum of irradiated and non-irradiated cod liver oil and of cottonseed oil in an attempt to see whether there was a correlation between the wave lengths particularly absorbed and those effective in curing rickets.

Hess, Weinstock and Sherman (1926 a) demonstrated that it is the sterol which is activated since while purified cholesterol and anhydrous cholesterol can be activated by irradiation, the watery filtrate cannot. Shear and Kramer and Kramer, Shear and Shelling have separated from irradiated cholesterol a yellow oil which cures rickets in rats both in crude form and cholesterol-free, the latter being the more potent. And Bills and MacDonald have recently pointed out that while in the activation of sterols both the double bond and the secondary alcohol group are involved, the former must be intact, though the latter may be replaced by certain acid radicals. Among the esters of cholesterol the acetate, isobutyrate and benzoate are readily converted into antirachitic modifications by the action of ultra violet rays. The substance activated is the ester molecule as such, and not the cholesterol liberated therefrom.

According to Hess, Weinstock and Sherman (1926 b), during irradiation cholesterol is being inactivated at the same time that it is being activated and thus presents a mixture of at least two forms, active and inactive. Activated cholesterol is separable into digitonin precipitable and non-precipitable fractions and the latter alone is active in healing rickets, constituting only about 4 to 5 per cent of the original amount. The specific antirachitic power of activated cholesterol is thus further linked with that of cod liver oil, which is due entirely to its non-saponifiable fraction, the potency of which is increased by eliminating a portion by precipitation with digitonin. The activity of cod liver oil is

probably due to irradiated food which the cod has eaten. Bills, however, suggests that vitamin D is synthesized by fish, since their principal food does not contain enough to account for the vitamin accumulated by the cod during its midsummer period of fattening and since it does not seem to be increased by irradiating cat fish nor decreased by keeping them for 6 months in the dark on a vitamin-deficient diet. Hess and Windaus have recently suggested that it is not the cholesterol itself which develops antirachitic properties through irradiation, but rather some contaminating substance intimately associated with it. They further report that ergosterol (an optically active sterol possessing three double bonds and a hydroxyl radical) when irradiated with a quartz Hg lamp has antirachitic action when as little as 0.003 mgm. per capita is fed to rats. Approximately 1 mgm. of cholesterol is needed to initiate healing.

Steenbock, Hart, Elvehjem, Kletzien and Riising found that the antirachitic properties of hays are related to their exposure to sunlight, clover hay made with exposure to sunlight showing considerable calcifying power in rats while clover hay made in the dark is inactive. Weathered hay shows a decreased antirachitic activity which may be increased by irradiation with a quartz Hg lamp. The old adage "to make hay while the sun shines" takes on a new significance. Goodale reports that a 10 minute irradiation with a quartz Hg lamp of dry chicken mash favored growth but did not wholly prevent leg weakness. Sunning the food for a half-hour did not further growth.

Hess, Weinstock and Helman suggest that the beneficial action of irradiating an animal is produced through the activation of the cholesterol in the skin, from where it is absorbed and circulated in the blood stream. This suggestion is rendered plausible by the demonstration that human and calf skin acquire antirachitic potency following irradiation as evidenced by feeding it to rats. A comparison between the relative protecting value of irradiating the animal, and the feeding of irradiated skin and of irradiated cholesterol, shows that, although irradiated cholesterol protects when given by mouth, the intensity of radiation required to bring about adequate activation is far greater than when the cholesterol is normally activated in the skin of the living animal (Hess, Weinstock and Sherman, 1925).

Gates and Grant found that the feeding of cod liver oil or of irradiated cholesterol to normal rabbits did not produce the characteristic changes in the relative weights of endocrine organs, notably the external parathyroids and the hypophysis, which follow irradiation of

the animal. And Koch and Cahan state that while cod liver oil in curing or preventing rickets raises the inorganic blood phosphate almost to normal, the direct irradiation of, and the feeding of irradiated cholesterol to, young rats has very little effect on it. They obtain low phosphate values and a low product of P and Ca in animals which, so far as roentgenograms demonstrate, show perfect bone calcification.

Numerous papers have demonstrated a correlation between antirachitic potency and photoactivity on one side and peroxidation on the other.

Respiratory metabolism. Under this heading will be considered the effects of radiation on the rate and volume of respiration, the irritability of the respiratory center, blood reaction, acid-base equilibrium, ionic equilibrium, CO_2 output, blood gases, basal metabolism, body and skin temperature.

The early literature on body and skin temperatures is very contradictory. The work of Sonne and of Loewy and Dorno on the relative penetration of different wave lengths and consequent heating of the skin and subcutaneous tissues as well as the influence on the general body temperature was referred to in the section on the skin. Koenigsfeld regularly observed a drop in rectal temperature of between 0.1 and 0.9°C. following even short (4 to 6 minutes) quartz Hg lamp irradiation periods, with drops in skin temperature of between 0.1 and 0.6°, though rises of between 0.1 and 0.2° sometimes occurred. Rosselet (Rollier, p. 203) states that the temperature of the skin may exceed 104°F. during insolation and, though the production of heat is a phenomenon in which the nervous system acts, that direct warming of the blood is also concerned in the rise of temperature which takes place during a sun bath. The duration of the exposure is important. In several cases it was found that after insolation for three-quarters of an hour the temperature was lower than before exposure, but one to two hours later it was equal to or higher than the original figure. At the beginning of a course of sun treatment the temperature curve falls sharply during the first two hours, beginning for example at 98.6°F., falling to 97.7°, and subsequently rising to 99.1°, the greatest variation being 1.6°. When the patient has become accustomed to the treatment the initial fall disappears, the temperature rising gradually to reach a maximum between noon and 2 p.m., after which it falls again.

Balderrey and Barkus report that the insolation of patients with some manifestations of tuberculosis produces a slight increase in blood

alkalinity, average of 0.05 pH, and most marked in those showing the deepest pigmentation. Essinger and György obtained in some cases an early tendency toward alkalosis, in others the reverse. Kroetz has summarized the work on the action of short waved radiation on the acid-base balance with particular reference to blood reaction. Irradiating blood in vitro increases its acidity. In the organism there is usually during the first hour a transitory increase in blood acidity, though sometimes an alkalinity is demonstrable at this time. Twenty-four hours later there is increased alkalinity disappearing slowly and sometimes lasting for 14 days. Fatal doses are always accompanied by acidosis. Man and animals, well and ill (tuberculosis and cancer), are apparently equally affected so far as their blood reaction is concerned, and the action seems similar from the short ultra violet to the hard x-rays. The CO_2 combining power behaves in two ways. In the early hours after irradiation it is lowered, later it is raised and remains high for several days. Only when the irradiation has been very severe, or nutrition poor with a marked loss of base, is the combining power lowered during the late periods. The alveolar CO_2 tension always drops slightly, 7 mm. Hg being the maximum. Hasselbalch believed that this was caused by a primary increase in pulmonary ventilation due to increased irritability of the respiratory center which reduced the free CO_2 in the blood. The fact that the acidity of the urine is not increased is in favor of this view. Ederer found that moderate doses of radiation increased alveolar CO_2 tension, while strong doses lowered it, independently of any action on the skin. He saw no argument for a variation in the irritability of the center, but regarded the increased CO_2 tension as due to a primary variation in the acid, or basic, valences of the blood resulting from a flow of base from tissues to blood, or to a reduced production of acid. Kroetz believes that both mechanisms play a part. He calls attention to the fact that irradiation produces marked shifts in the serum acid-base ratio as well as shifts in the body minerals. The initial transitory hypocapnia is characterized by an increased flow of acid into the blood, the later and long lasting stage of alkalosis by an over-compensatory action on the part of the base shifting tissues. The acid stage is due to the formation of undetermined acid valences, and occurs also during the cases of immediately increased CO_2 combining power and alkalosis. Morna and Reed failed to find any constant changes in the CO_2 combining power of dog blood following C arc irradiation of it as it flowed through a quartz tube interposed

in the carotid artery. But the animals were anesthetized and the blood was heparinized in vivo. de Gheldre, on the other hand, reports that ultra violet irradiation diminishes the alkali reserve of rabbit blood.

Hasselbalch studied the influence that long continued irradiation with a large C arc (150 A) had upon respiration and other functions from the point of view of a climatic factor, the effects of which are observable not only during the actual irradiation, but for several days thereafter. There was no observable effect until the resulting erythema made its appearance, at which time there was a decrease in the morning frequency of about 10 per cent, lasting for 6 to 7 days following a single irradiation and after the erythema had disappeared. The volume of air breathed increased so that in proportion to the decrease in frequency ventilation remained practically constant. The cause is referred to cutaneous vasodilatation, and the irritability of the respiratory center to blood CO_2 tension is believed to be temporarily lowered by the depression of the cutaneous vasomotor system.

Hasselbalch and Lindhard later investigated the respective parts played by the reduced barometric pressure and increased ultra violet of high altitude. The frequency was found to increase as barometric pressure decreased, but with increased ultra violet action, even only on the face and hands, it rapidly dropped to below the usual sea-level rate. The amount of air breathed was but little influenced by drop in barometric pressure, while the action of ultra violet produced a marked increase and as the altitude was lowered this decreased, in correspondence with the increased barometric pressure and the decreased ultra violet. The decrease in frequency and the increase in volume of air breathed is thus not an adaptation to high altitude, but an effect of the increased ultra violet of sunlight. In Lindhard the increased solar ultra violet led to a marked decrease in alveolar CO_2 tension, while there was no effect on Hasselbalch who was acclimated. The irritability of the respiratory center increased with increasing altitude, to eventually become subnormal after acclimatization, but the action of ultra violet further increased it, the increase coming after the decrease in alveolar CO_2 tension due to the over-ventilation produced by the lowered barometric pressure. It would be interesting to have a repetition of this kind of work.

Lindhard held that sunlight is the climatic factor which exercises the determining influence on respiration during the course of the year, the annual fluctuations in alveolar CO_2 tension being ascribed to the action of sunlight through an increase in the excitability of the center to CO_2.

Sunlight was also considered the determining factor giving mountain climate its special character. Lindhard found that from mid-winter to summer the excitability of the respiratory center to CO_2 increased, the alveolar CO_2 tension decreased by an average of 11 per cent, the frequency of respiration by 24 per cent, while alveolar ventilation increased by 15 per cent, expiratory volume by 26 per cent, ventilation quotient (alveolar ventilation in liters per minute, divided by alveolar CO_2 tension in mm. Hg) by 29.3 per cent and the consumption of O_2 and the production of CO_2 by 4 and 5.5 per cent respectively. The changes were similar to those observed in Greenland and on mountain tops, and those produced by the action of C arc irradiation.

Durig, von Schrötter and Zuntz found that intense illumination does not markedly change basal metabolism, the most outstanding phenomenon being a lowering of alveolar CO_2 tension and in many an increase in ventilation. These authors did not feel that increase in illumination has much to do with the effects on the respiration observed at high altitude.

Hill and Campbell (Hill, p. 114) conclude that the rise in metabolism caused by heliotherapy per se is insignificant when compared with that caused by exposure to open air. At high altitude the increase in calories (59 to 225 per cent above basal) is due to the exposure to the higher atmospheric cooling power. Häberlin, Kestner, Lehmann, Wilbrand and Georges point out that though appetite and growth are improved by the North Sea-shore climate, gaseous metabolism is not specifically increased. The metabolism determined inside the house and in the open, lying naked on the sand, usually shows an increase for the latter, dependent it seems upon chemical regulation of heat loss. The increase is observed when the sun is not shining as well as when it is but always occurs when there is a wind, so that it is most probably due to skin stimulation. Kestner (1923) and his co-workers found that sea-shore sun (and quartz Hg and C arc lamp radiation) itself strongly and immediately increases gaseous metabolism by its action on the skin, though the increase is diminished if there is a simultaneous heating effect which brings the chemical heat regulating mechanism into action. The effect is specific, being called forth by a stimulus to the skin. Kestner (1925) and his co-workers report that basal metabolism was increased at high altitude in winter but not in summer and although it also occurred in the absence of sunlight it was much greater when the hands and face were exposed to the sun.

Knipping concludes that while in the majority of cases basal metab-

olism is increased during the first weeks in the tropics, it is depressed after a longer stay, so that the basal metabolism of Europeans in the tropics and of Malays and of Southern Chinese is lower than the average Benedict figures. During solar irradiation the gaseous exchange is never increased more than 10 per cent, the R.Q. is always small, and the body temperature does not rise above 36.5°C. In agreement with Häberlin and others, approximation to the sea coast was always found to deepen respiration for which the increased amount of solar radiation was held chiefly responsible. The mere fact of going from a temperate climate to the tropics produced a decrease in frequency averaging between 2 and 37 per cent, with an increase in volume between 1.5 and 4.1 per cent for which the greater purity of the air is believed to be responsible. The percentage increase in O_2 consumption does not approximate the percentage increase in minute volume, due to special conditions imposed upon the heat regulating mechanism by the high temperature, humidity and lack of air movement. Eijkman thinks that basal metabolism does not vary with the climate or the race. He compared Malays and Europeans in the Dutch East Indies and found that in a condition of rest and of moderate labor the metabolism and heat production were the same in the two races and not more in a cold climate than in a hot one. But Sundstroem believes that basal metabolism is decreased in the tropics, a higher rate coinciding with cooler weather, a lower one with muggy. In addition, the alveolar CO_2 tension is decreased, the lower values coinciding with a cool, dry and sunny period, while the peak of "tropical alkalosis" comes at the height of the hot season. Hafkesbring and Borgstrom demonstrated that the metabolism of individuals living in New Orleans is definitely lower than the DuBois, Harris-Benedict and Dreyer standards. Other studies have shown that the caloric intake in the south does not vary much from that of the north but the protein intake is lower.

According to Fries the improved appetite and weight of malnourished children following quartz Hg lamp irradiation is not due to a concomitant rise in basal metabolism, since the basal metabolism of children during months of treatment and non-treatment shows no appreciable differences. Harris claims that, although the total radiation from either the iron arc or the quartz Hg lamp has no effect on metabolism, there is a group of rays (436–291 mμ) which has a marked and immediate effect upon the metabolism of rats and mice, an increase of 20 per cent in CO_2 output being observed. Heat production is decreased by exposure to the mixed rays, more so in pigmented than in albino animals,

though the pigment has a high absorption power. Campbell, however, found that there was no increase in the metabolism of healthy men, mice or rats when exposed to the quartz Hg lamp through blue uviol glass. No effects were produced by the total rays (223–770 mμ) the visible (400–700 and 400–436 mμ) or by the ultra violet (mainly) rays.

Eichelberger observed no effect on basal metabolism following solar and C arc radiation and no influence on the rate and depth of respiration. Mason and Mason irradiated human subjects with a quartz Hg lamp. The cases were divided into two groups, those with a marked degree of pigmentation and those with an increased amount of circulating bilirubin (pernicious anemia and catarrhal jaundice). Both groups showed marked reduction in heat production, pulse and metabolic rate, the second more so, possibly because the bilirubin sensitized them, the lowering of heat production preceding the development of pigmentation. Feeding buckwheat to a subject who had failed to show a lowering of metabolism after multiple exposures resulted in a subsequent definite fall, without toxic symptoms and skin manifestations.

According to Bodine, changes in muscle tonus in an insect are associated with corresponding changes in the rate of CO_2 output. If the eyes of grasshoppers are covered, which decreases muscle tonus, there is a 30 to 40 per cent decrease in the rate of CO_2 output, lasting as long as the eyes are blackened. Sonne reports that quartz Hg lamp irradiation of meal-worm chrysalids increases O_2 consumption by about 40 per cent. When a glass filter is interposed the increase is only 20 per cent and when a glass and methylene blue filter is used the increase is only 10 per cent. Yellow light has no influence on gaseous metabolism. The increase in O_2 consumption continues for some time after the irradiation with an average value of 15 per cent if the unfiltered radiation was used, but filtering out the essential ultra violet frequencies abolishes the after effect. Crofts and Laurens found that while the frog was sensitive to change in illumination as exhibited by an increased rate of respiratory movement, the amount of the increase bears no quantitative relation to wave length, and the effect is transitory, the rate returning to normal in two minutes. The increase leads to an increase in CO_2 produced, not always greater in the light than in darkness, which is simply a result of the stimulus (the change) and not a specific effect of light.

Mode of action. It is evident that, while we are in possession of an enormous amount of information concerning the results of irradiating man and animals, normal and abnormal, we are not yet ready for

explanations and generalizations, and no unitary hypothesis as to how the results described are obtained can yet be formulated. We still stand in need of facts obtained under definite, controlled conditions of dosage, intensity, wave length, etc., on normal and abnormal organisms and when sufficient quantitative data have been thus obtained a theory will develop as a matter of course. Nevertheless, we can call attention to some of the outstanding points that have been made, not expressing a final opinion, but merely laying emphasis where it seems justified.

Many of the claims made for the use of radiation are still based upon empiric evidence and practical applications are made without scientific support because the fundamental principles of the biophysics and physiology of radiation are still unsolved, and the real action of radiation on the living cell is still unknown. Irradiation with the wave lengths that we are interested in has two effects, stimulative and lethal. In general the first is exerted by wave lengths to as short as about 290 $m\mu$, the second by those shorter. Finsen at first thought that the radiation with which he cured lupus acted as a bactericide. Later the question arose as to whether the radiation did not rather act as a stimulant to the tissues than as deadly to the bacilli. In the action of radiation we have two elements, a photochemical effect, which ends with the production of dermatitis and its logical effects, and a biological, which may last for some time.

Hinrichs has briefly reviewed the various views as to the action of ultra violet radiation. It produces primarily a surface effect, it inhibits the action of hormones and enzymes; it kills protoplasm by coagulation and not by the inhibition of enzyme action; its effect is due to sensitization to heat; its action interferes with the time relations in a system of interdependent, progressive processes; its effect is due to the precipitation of the proteins of protoplasm following electron emission; certain constituents of protoplasm, as tyrosin and phenylalanin, act as optical sensitizers rendering living cells susceptible to the toxic action of ultra violet radiation.

At one time there was considerable argument as to whether ultra violet radiation could act directly on deep seated organs, and there are still some who believe that this is the case. The only reasonable conclusion, however, is that following ultra violet irradiation some photochemical substance formed in the skin is carried by the blood stream to these various organs, there bringing about the observed changes. Rosselet and Rollier, however, do not believe that the direct action of radia-

tion, as on a deep-seated tuberculous lesion, has been proved or disproved and therefore cannot be denied. But indirect action is well founded in fact. According to them light absorbed by the skin gives rise to numerous and useful reflexes; absorbed by the blood the energy given out by the radiations is stored and carried in the blood stream to every part of the body, stimulating, when liberated, the intracellular processes of oxidation and reduction. The sun bath by dilating the capillaries activates the circulation and may induce a continuous tonic action on the sensory nerve terminals in the skin, thus restoring tone to muscles and promoting physiologic processes throughout the body. This is the probable explanation of the increased metabolism of the body, of the improvement in general health and of the increased resistance to disease. But Saleeby believes that it is not the sun which so acts as to improve and maintain muscular tone, but the cold air that stimulates the muscles, maintaining their tone and by their metabolism maintaining the body temperature. The virtue of sea-bathing, as an adjunct to heliotherapy, is thus equivalent to cold alpine air. Hill, Kestner, et al., report similar results and conclusions.

The majority of reactions caused by radiation are due to oxidations and reductions, or processes in which changes in valency take place and there is some evidence to show that the biological action of short waved radiation is due to its reducing properties, to the splitting off of O_2 molecules from the easily deoxidizable plasma compounds.

The therapeutic action of radiation has been regarded by some as due to heat produced locally by absorption. This local production of heat speeds up certain changes with no harmful raising of body temperature. Sonne (1921) holds that the view that the therapeutic effect of the universal light bath is essentially due to the ultra violet rays is not sufficiently warranted. Based on the specific absorption relations of the "visible heat rays" during irradiation of the human skin the following theory is advanced: the curative effect of the universal light bath (arc lamp) is due to the capacity of the luminous rays to heat a very essential portion of the aggregate blood volume of the organism to a temperature possibly exceeding the highest ever measured fever temperature, without causing the body temperature, owing to its heat regulating capacity, to rise to any measurable degree. The specific heat of this blood circulating in the organism acts as a curative agent. Sonne's facts concerning the relative absorption and heating effects of the luminous as contrasted with the infra red rays have been verified by Hill, and by Loewy and Dorno. Kestner, Kimmerle and

Knipping believe that the action of radiation on blood pressure and the formation of red cells and Hb is through the breathing of nitrous oxide formed by the arc lamp as it burns and by solar radiation in its passage through the atmosphere. We have not been able to substantiate this view and Rothman shows that the lowering of blood pressure is due neither to the gases respired nor to cutaneous hyperemia.

The rôle of the skin pigment has been discussed by many authors, along with that of cutaneous hyperemia and erythema. Rollier believes that short, lethal wave lengths are transformed by the fluorescent action of pigment into long non-lethal wave lengths thereby increasing the depth of penetration and the intensity of reaction. As we now know, however, pigment is non-fluorescent (Clark, 1922, Saleeby and Peacock). Rollier is convinced that patients undergoing the sun cure who do not pigment readily do less well than those who do. But many others have not found this correlation between pigmentation and light effects, the amount of pigment, at most, serving merely as an index of the reaction of the body to the radiation.

Pigment assists in the absorption of energy,—the skin being less reflective after pigmentation than before—which is transformed into heat. Pigment may thus be regarded as a black body transforming chemical energy into heat and absorbing all radiation, the pigment representing innumerable little available collections of heat energy. Heliotherapy is thus nothing other than simple heat-therapy by radiant heat. Balderrey and Ewald show that increased pigmentation is not only a protection for the body against the irritating effects of the short waved ultra violet, but that it also increases light penetration, heat absorption, heat production and heat radiation. They demonstrate that pigmentation of the skin accelerates and augments the photographic action of radiant energy passing through parts of the human body, thus favoring the penetration of energy by changing a white reflecting surface to a dark absorbing one.

Hill and his co-workers have clearly demonstrated that melanin acts as an absorption screen, not as a sensitizer or transformer, the energy absorbed being converted into heat. By this conversion the sweat glands are stimulated and the moisture acts as a further protection. Owing to pigment the black man can have a thinner skin and so lose heat by convection more easily; he also is excited to more active sweating than the white man.

Rothman follows Jesionek in producing pigmentation by gradually increasing doses, rather than in producing a dermatitis by massive

doses repeated at intervals. But, on the other hand, the unimportance or undesirability of pigmentation as contrasted with extensive cutaneous hyperemia and erythema is stressed by many, Finsen, Hasselbalch, Reyn, Humphris, etc., but Hausmann doubts whether there is any connection between inflammation and therapy.

Another view regards the various effects as due to chemical changes in the skin which bring about influences on distant parts either by reflex action, stimulating sensory endings in the skin, or by diffusion into the blood stream and transport to the parts affected. Breiger considered the changes brought about in various skin conditions (infections and wounds) and in extrapulmonary tuberculosis as due to internal influence started by reflex action. Harris, in connection with the widespread peripheral vasodilatation produced by ultra violet radiation, states the view that ultra violet is a cutaneous irritant manifesting itself by sensory and vascular phenomena involving axon and distance reflexes. Rothman correlates the effects which he observed soon after irradiation was begun,—lowered blood pressure and blood sugar, increased sugar tolerance and decreased adrenalin secretion,—with depressed sympathetic tone started by stimulation of cutaneous sympathetic endings.

Pathological researches have shown that cellular degeneration is a frequent sequel to irradiation of tissues, the degeneration consisting in various abnormal features appearing among the cells at differing times after irradiation. The changes in structure may be due to direct action upon the internal constituents of the cell or to some interfacial action. Ultra violet radiation, we know, produces degeneration of epidermal cells, characterized by pyknosis of the nuclei, contraction, homogenization and probably coagulation of the protoplasm. The action of ultra violet rays leads thus to the absorption of damaged cell products and calls up a response on the part of the various defensive mechanisms. Excessive action floods the body with too much of the products of tissue damage. Lewis and Zotterman have shown that the action of ultra violet radiation on cutaneous vessels like other agents, such as freezing, burning, etc., which cause tissue injury, sets free in the skin vasodilator substances with histamine-like action which diffuse into the surrounding skin to be then conducted away by lymphatic channels. The vessels become dilated because they lose contractile power and are more or less irresponsive to vaso-constrictor substances and to histamine. Kroetz believes that in the action of radiation the getting into the circulation of protein decomposition products is the

outstanding event and that the hormonal and autonomic system changes are simply the result of the shift in mineral balance.

Reflex action may explain in some cases how internal organs are influenced by the action of radiation on the skin, and there may also be some change in the capillary blood which has absorbed the energy, but the greater part of the effects of irradiation must be produced by chemical means, by substances formed in the skin by the action thereon of radiation. These are the end products of damaged and killed cells, or the result of increased activity on the part of the basal cells of the skin, or an activated substance, or substances which get into the circulation and are thus distributed to all parts of the body.

Intestinal absorption plays an outstanding rôle in the effects of radiation. In rickets, irradiation is followed by a decreased bowel excretion of Ca, the healing being bound up with increased ability to promote absorption from the intestine. During active rickets considerable amounts of Ca and P are absorbed from the bowel and re-excreted into it and irradiation also prevents much of the abnormal re-excretion. It is evident then that the action of radiation on the skin alters the physical and chemical conditions of the blood. The mechanism by which the absorption from the intestine is increased is influenced by two factors, the reaction of the gastro-intestinal contents and the fat intake, as in cod liver oil. Alkalies diminish mineral absorption while acids increase it. In infantile tetany the pH of the gastric contents is increased, with consequent decreased Ca absorption, and returns to normal with the disappearance of the symptoms. The absorption of Ca is initially dependent on the free acid of the gastric juice affecting the solution of Ca salts in the diet, and is normally restricted by the alkaline reaction of the intestinal secretions which tend to neutralize and so precipitate lime as insoluble phosphate. The absorption of P occurs freely even under pathological conditions and is difficult to restrict except by the addition of a large excess of Ca to a diet relatively poor in P. The fixation of P in the skeleton is dependent on that of Ca and in a diet unbalanced with regard to the mineral elements the absorption of an excess of P is followed by its excretion in the urine (Telfer, Grayzel and Miller). According to Grant and Gates the parathyroid glands are directly concerned in the processes connected with the influence of ultra violet radiation on Ca metabolism. One result of exposure of the skin to ultra violet is some alteration in the composition of the blood to which the parathyroids are sensitive and to which they react by hypertrophy. This, if accom-

panied by an increase in functional activity, tends to counteract, among other things, the failure of the intestines in regard to the absorption and retention of Ca with consequent low Ca level in the blood.

The recent work on the activation of foodstuffs as well as of animal tissues and products points to a possible mode of action through the production of an active substance in the skin following irradiation which circulates in the blood stream. Weinstock and Helman have suggested that the substance activated is the cholesterol in the deeper layers of the epidermis in close approximation to the prickle cells. A comparison between the relative effectiveness of irradiating an animal itself, where the activated cholesterol can be absorbed from the skin in a physiological way, and the feeding of an activated inert substance shows that in the latter instance the amount of irradiation which is required to bring about adequate activation is greater than where the cholesterol is activated under normal conditions.

In connection with the activation of skin cholesterol recent work showing that the efficient agent can be absorbed otherwise than through the intestinal wall is of major importance. It has been reported that intraperitoneal injection of cod liver oil affords partial protection against a rickets producing diet and improves growth and calcification in rats on a deficient diet. Further, that gauze pads saturated with cod liver oil applied to the abdomens of infants and renewed daily produce an increase in the inorganic P of rachitic children in from 2 to 3 weeks of treatment. Kramer, Kramer, Shelling and Shear found that when cholesterol-free cod liver oil concentrate suspended in ether was subcutaneously injected it cured rickets, the antirachitic substance being as potent, provided a suitable vehicle is used, as when given orally; and Wilkins and Kramer report that the intramuscular injection of an ether concentrate of cod liver oil is followed by the same changes in two children with active rickets as are usually observed following the oral administration of cod liver oil. The increased absorption of Ca and P from the intestine is thus but the local demonstration of a general influence exerted through the circulation.

One conception of the effects of radiant energy upon living matter is that the heat effect is due to increased molecular motion while the "abiotic" or lethal effect, exerted by wave lengths shorter than about 295–300 mμ, is due to direct atomic disintegration of the molecules with immediately resulting chemical changes. The effect of radiation of given wave length is directly proportional to the coefficient of absorption of the protoplasm for that wave length. All radiation transfers

energy to molecules which absorb it and produce heat, but certain frequencies fall into step with the oscillation periods which depend on the molecular structure and so break up the molecule when the energy absorbed is sufficient. The particular kind of radiation which produces this direct action depends on the character of the molecules.

Baly has suggested that before any chemical reaction can take place the substances taking part in it must acquire a certain amount of extra energy. The living organism seems to have the power of utilizing the energy of ultra violet, and Baly believes that a vitamin is a substance which depends for its properties upon the fact that it has taken up an excess of energy from ultra violet or other source which may be liberated and thus facilitate certain fundamental chemical reactions in the body.

Bovie and his co-workers demonstrated that rays from widely separated regions of the spectrum, provided their ability to penetrate the organism is such that similar parts are radiated, produce similar physiological effects regardless of the difference in wave length. In other words, it is the instability of the physiological mechanism rather than wave length which determines the nature of the physiological effect produced. They postulate, therefore, that the differences observed in physiological effects are due to differences in penetrating power rather than to any action specific for wave length. In the visible and ultra violet regions absorption depends upon molecular composition, in the Roentgen and gamma regions upon the atomic composition of the irradiated protoplasm. The visible effects of irradiating amoeba with 280 mμ are described as those that would be expected if there is some structural organization in the protoplasm that gives way to the stresses put upon it. The absorption of this radiation is accompanied by the atomic rearrangement of chemical change. If the disorganization of function is carried far enough the molecular organization, which is dynamic and which has its origin at the colloidal interspaces, breaks down and cytological changes result.

Clark has given a theory of the action of radiation based on atomic structure, configuration of electrons, etc. The physiological effects have their origin in the photochemical reactions produced when radiant energy is absorbed. All photochemical reactions are initiated by a change in configuration and velocity of the electrons of the substance absorbing the radiant energy. If the incident energy has small enough wave lengths to produce vibrations in the electrons, instead of in the molecules and atoms, its absorption may result in the activation of

electrons. The activated electrons may be ejected from the molecule as the result of absorption of energy, in which case the molecule is ionized, or they may be displaced to an outer orbit in which case the atom or molecule is activated. In either case it will show altered chemical reactions. Clark elaborates a theory of the formation of images on photographic plates which in its application to the living cell may be summarized as follows: Energy shorter than 300 mμ acts on the living cell by ionizing its photo-electric constituents thereby leading to photochemical action. Energy longer than 300 mμ acts in the same way in the presence of sensitizers which so affect the surface conditions of these constituents that their photoelectric threshold is shifted into the visible, and they therefore become ionized with resulting chemical action when illuminated by visible or near ultra violet energy.

Clark has shown that normally only a part of the blood Ca is present in ionized form, the remainder being in combination with the blood proteins. Serum albumin, at the pH of blood, carries a negative charge which it loses when irradiated with a quartz Hg lamp. If the unionized Ca is bound electrically by the negatively charged proteins then the radiation by discharging these proteins should free some of the bound Ca, thus increasing the percentage of ionized Ca and accounting for the influence of radiation on metabolism, since it is the ionized Ca which is of importance in maintaining the ratio between Ca and P. In a paper dealing with the coagulation of egg albumin Clark gives evidence that the changes in viscosity and surface tension are probably associated with a change in charge due to loss of electrons on irradiation, or with a change in state of aggregation or both. According to some (Perrin, Bovie, etc.) all chemical reaction is accompanied by both the absorption and the irradiation of energy, the speed of the reaction being determined by the radiation intensity. Saidman reports that a man loses a negative charge more quickly when irradiated with a quartz Hg lamp than when simply remaining in ordinary room light. Koenigsfeld and Hill likewise believe that the action of radiation consists essentially in the setting free of electrons which leads to cellular disturbance and upset of chemical equilibrium. The pathological action of radiation consists in the knocking down of the entire arrangement of the electrons so that their proteins attain an isoelectric state and coagulate.

But even if the effects of irradiation are photoelectric it is clear that radiation produces some substance or substances in the skin which

eventually pass to the blood, so that all the observed effects are the expression of photochemical change.

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THE PHYSIOLOGICAL EFFECTS OF ROENTGEN RADIATION UPON NORMAL BODY TISSUES

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Since Wilhelm Konrad Röntgen, in 1895 (133), announced his discovery of a new type of radiation, there has developed a voluminous literature which is entirely devoted to the use of this new agent in the treatment of malignant disease and other abnormalities of the human race.

We are concerned here with the physiological effects of roentgen radiation (x-rays) upon body tissues—the local and general, acute and chronic effects being considered in conjunction with the three major (gross) divisions of radiation, long wave lengths, medium and short wave lengths, the so-called soft, medium and hard rays respectively. For the sake of brevity, all data about bacteria, protozoa and plants are omitted unless pertinent to the discussion. A consideration of the effects of radiation upon neoplasms is avoided because this is a special field in itself, necessitating critical examination of controls, methods, etc., far out of the scope of this review. Due to the large amount of literature upon the subject of radiation and because of the added complication of the consideration of beta and gamma radiation, distant and local effects, filtration, etc., it was thought wise to omit all of the experimental work done with radium.

Some of the earliest and best work was done on the skin by Destot in 1897 (40), and on the testes of rats by Bergonie in 1906 (11). Regaud and his collaborators in 1912 (129) studied the effects of soft roentgen rays upon the skin, the stomach and the gastro-intestinal tract, showing the production of chronic, non-healing ulcers in all three places. About this time physicists began to be interested in the field of biology, and the biophysicists began to play an important part in supplying necessary information to the therapist. The advent of the Coolidge hot filament tube in 1914 (27) was another distinct advance, as this made available a constant source of radiation which could be

duplicated, fairly well controlled and which would yield amounts of radiation previously unavailable to the therapist or experimenter with the gas tube. About 1917–1918 further improvements in the development of roentgen ray machines placed in the hands of the therapist a new type of radiation of very short wave length, approaching closer to the gamma radiation of radium than anything previously obtainable.

For a general review of the field up to the advent of deep therapy the reader is referred to the book of Colwell and Russ (26) which discusses the effects of long and medium wave lengths upon body tissues; for the effect on the ovary, the embryo and the fetus, the book of Dorland and Hubeny (46), and the experiments of Wagner (156), Ancel (1, 2) and Mavor (101), and for the effects upon heredity, the publications of Bagg (5, 6). There is a good review of the German literature by Kuhlmann (83), with a critical discussion of the general effects of radiation from the German point of view.

We are concerned therefore with a discussion of the effects of roentgen radiation upon body tissues, considering primarily normal structures, though data obtained by radiating abnormal tissues are included when evidence has been obtained in contrast to the normal. Some of the material has been obtained directly from patients but in the main most of the data has been collected from experiments upon animal tissues. The normal variants in laboratory animals must always be kept in mind, differences due to species must be allowed for and caution used in the application of the results obtained from various animals as a guide in the use of roentgen radiation as a therapeutic measure for the patient.

In order to discuss the physiological effects of radiation, we must know the relative penetration and absorption of various wave lengths of radiation from various portions of the roentgen ray spectrum. It has been pointed out by many authors that these rays must be absorbed in order to be effective. This brings into the discussion a well known physical problem that there are at least three things which may happen to a beam of roentgen radiation. It may penetrate completely the tissue, it may be absorbed entirely; it may excite so-called secondary rays of relatively the same order of magnitude though probably of longer wave length but of relatively little penetrability. The latter are thought to be the main factors in the production of the physiological effects in the body tissues (Clark, *Applied X-rays*, 1927).

The relative amount of a roentgen ray beam which may be absorbed by superficial layers of the body tissues is determined by its wave

length (60, 69, 70, 121, 122). In a way, the wave length determines the gradient of penetration and absorption established. The longer the wave length the more radiation is absorbed (the more effective the gradient). There is a gradient of penetrability also. With relatively long wave lengths, the first tissues struck by the entering portion of the roentgen ray beam are effective to a great degree in absorbing all of the energy. The shorter the wave length, the less there is absorbed and the more radiation becomes available to the deeper organs and other structures in the path of the beam. In other words, the relative absorption of radiation of various wave lengths by a particular tissue decreases with the wave length. Paradoxically, this is of considerable assistance in therapy, but is of value in radiography only up to a certain point. In radiography, the absorption of radiation by denser structures produces the contrasts in the photographic film. The absorption of radiation by a tissue determines its relative opacity to the beam of radiation and that wave length is used which will give the maximum contrast between two tissues of unequal density.

All of these factors make it necessary that we know and take into consideration the average wave length of a particular beam of radiation. This is determined by the potential at the tube terminals (49), which should be measured in kilovolts by a standardized sphere gap connected in parallel with the tube. The average wave length can then be calculated from a chart for the particular metal making up the target and should be compared with or standardized by actual spectroscopic measurements. Measurements made with point gaps vary with the humidity and the sharpness of the points and are not comparable. No two machines until recently, perhaps, can be trusted to produce the same quality and quantity of radiation at the same settings (23), and the general lack of standardized equipment for measurement of the output makes it very difficult to compare and evaluate the experimental results obtained by the various authors.

It is obvious that experiments performed with long wave lengths (low voltages) or so-called "soft radiation" may give results different from those using the shortest wave lengths (high voltage) or the so-called "hard radiation" of deep therapy, which has great penetrability. In between these extremes lies the medium wave lengths of medium therapy. The "soft x-rays" are produced by potentials up to 50 kilovolts, medium wave lengths between 50 and 150 kilovolts and hard x-rays from 150 to 250 kilovolts.

Practically all of the work done with the gas tube comes under the

group of "soft x-rays." In experiments done previous to 1918, either long or medium wave lengths were used. Since then there is considerable confusion, because, frequently, the wave lengths used are not stated and either very soft or very hard roentgen rays may have been used.

The terminology and standardization of the unit dosage of radiation has not been worked out and accepted. The problem is not so simple as that for radium because of the inconstancy of the output of "x-ray" machines. Ionization measurements may be suitable when standardized for one voltage or wave length but are not feasible at present for comparisons of dosage at different wave lengths (8, 9, 20, 60). Knowing the kilovoltage (the average wave length) and the amount of ionization in electrostatic units, the unit physiological dosage of radiation is capable of a rough estimate for the particular wave length and equipment. Another rough dosage unit which has had almost universal usage until recently, is the product of the intensity and the time expressed as milliampere minutes. This may be of sufficient accuracy for a particular institution but because of variations in machines and equipment is not suitable for comparison with the data of other institutions.

These measures of radiation bring us down to a still greater variable, the skin erythema dose. This quantity depends upon the various wave lengths, and of course, the distance of the target from the skin, whether or not filtration is used, and the kind and amount of the latter. The purpose of the filter is usually to remove the softer, or longer, less penetrating wave lengths from the beam and to make the constituents of the beam more homogeneous (49). A few millimeters of aluminum (1 to 10 mm.) cut out the very long and leave the relatively long or medium wave lengths in the beam. Copper and zinc ($\frac{1}{2}$ to 2 mm.) are used for producing uniform beams of the very short wave lengths.

In addition to the physical variables in the consideration of a skin unit dose, there is a marked physiological variation which is of very great importance to the therapist, though probably of less importance to the experimenter. In human beings the amount of radiation necessary to produce just a mild erythema of the skin at from 6 to 18 days after exposure, seems to depend upon the amount of pigment present and the relative thickness of the skin. That dose of radiation which will produce a mild erythema on the inside of the thigh or forearm in a thin-skinned blond, may cause no visible change in the skin of a dark brunette. The palms or soles or back of the neck can tolerate much more radiation than the dorsal surface of the forearm, without showing

an erythematous reaction. The necessity of knowing the exact tolerance of a particular skin area is of course of great importance in therapy.

The biological unit of radiation has been very difficult to establish, because of the lack of suitable measuring devices, the use of varying wave lengths of radiation and the natural variation in the reaction of the biological material used. The skin, being the most common available biological material, has been taken as the standard of comparison for therapy. This has been a practical and necessary research, for by its establishment the danger of serious injury to the patient is eliminated. All rational therapy is limited by the tolerance of the skin. All comparison of experimental results with clinical empirical experience has been made and necessarily so, upon the basis of the human erythema dose. The *erythema dose* has been generally taken as that amount of radiation which will cause a slight reddening or an erythema of the skin area radiated, within one to three weeks after exposure. This amount may not be followed by a tan. The maximum amount which will be tolerated without a visible erythema, though epilation may occur, is called a suberythema dose. As the dosage varies with the area of skin radiated and the region, and from person to person, it can be seen that this is rather unsatisfactory as a standard. The reason why most authors (66) are reluctant to forego the erythema dose as a biological unit is because there is no definite standardized actual measurement of the radiation which is yet acceptable for all wave lengths. The erythema dose as a standard is very unsatisfactory at best, because no two authors can determine what is the same stage of erythema, what is burning, what is tan, etc. (66), (71). Schall (136) in a series of 50 children of 13 years of age, studied the relationship of the skin dose to pigmentation, and to the physical dose. He was unable to show any constant direct relationship between the wave length and the physical dose, as measured by the reaction of the skin, because of the very great variation of the skin changes, as high as 140 per cent. Martius (98) does not agree with Grebe (60) that the biological effect of x-rays of different wave lengths depends upon the amount of energy absorbed because of the fact that soft rays have a much greater biological effect than hard ones. Yet with quantity and quality compared in respect to the erythema dose, the changes produced in so far as can be determined by the clinical and experimental data available are of the same relative type or order (100), (163). The erythema dose (E. D.) has been measured by means of pastiles and stated in terms of X or H units in the past, but is now more commonly spoken of as skin unit dose

(S. U. D.), Haut Einheit Dosis, (H. E. D.), erythema dose (E. D.) and dosage stated as fractions or multiples of the erythema dose (usually in milliampere minutes). An attempt is being made to standardize the erythema dose by ionization measurements with rather indifferent success so far (8, 9).

In trying to evolve a biological unit suitable for general use, plants (73), unicellular organisms, parasites or any other material available for this purpose have been radiated. Packard (114), in a very good review of the subject, discusses quantitative relationships of roentgen ray doses in experiments on seeds or eggs of various types. He points out that the normal variability in seedlings and material of this sort is large enough to account for the differences in the many reports published. He recommends the use of the fruit fly (drosophila) as a biological standard because of the constant susceptibility, averaging 97 per cent of all eggs. Their eggs freshly fertilized, are especially susceptible to roentgen rays, but the old eggs are quite resistant. Packard used these eggs in an attempt to demonstrate the inverse square laws and found that the results with both 160 and 190 K. V. were quite consistent, with various arrangements of distance, filtration and quantity. He came to the conclusion that if the total intensities were the same, the death rate of the flies would be constant, regardless of the type of filter or wave length used. He described in detail the technique for breeding these flies.

Plants have been used by many in an attempt to prove that roentgen radiation has stimulative powers. Ancel (3) and Esdorn (52) showed that there are many errors in experiments done with plants; that there is no definite evidence in favor of stimulation; and that there is considerable variation in the sensitivity of individual structures of the plant to radiation; and that the water content also has an effect upon the sensitivity. Thus very large numbers (thousands of seeds) should be used to compensate for the normal variation. New or young structures, in other experiments, were more sensitive than older ones; the latent effect was not truly present, as immediate injurious effects of radiation could be demonstrated.

Czepa (31), Pordes (122) and Desjardins (38) have all defined stimulation as something which produces an alteration in the condition of the living substance. As radiation is known to cause injury to cells and the use of the word stimulation should involve any change brought about in the cell by some agent, then cell injury is necessarily a cell stimulus brought about by radiation. However, in the literature of

this particular field, stimulation is assumed to mean a speeding up of the usual cell processes without especial detriment to the cell functions or activities. Thus Murphy (109) has been able to increase the number of lymphocytes by minute amounts of soft radiation and Packard (114) to increase the maturation through adult life of the fruit fly although its life span is shortened. Many have shown the production of rapid division of cells following radiation but this must be a primary reaction to cell injury and a repair process. As the definition of indirect stimulation is not clear, and is often confusing, the use of this term should be abolished. Further discussion of stimulation by radiation would only be controversial as the facts in its favor are meager.

After these general considerations, a more detailed examination of the particular effects of radiation upon the body structures can be made. Knowledge of changes in the skin brought about by radiation are of prime importance. In spite of considerable work done upon this subject, the actual sequence of events transpiring in the skin following radiation is very little known.

It is hard to distinguish the effects due to the changes in the epithelial cells of the skin from the secondary changes brought about by injury to the subcutaneous capillary bed. Regaud and his associates have studied most consistently the changes occurring in the skin, and although their investigations were undertaken with radiation of relatively long wave length, the changes described probably hold to a great extent for the other wave lengths.

The basal cells of the skin, or Malpighian layer (127) are the most sensitive and show vacuoles and pyknosis and lack of staining power after large doses of radiation. Gradually the rete of the dermis disappear and the base of the skin becomes flattened. As the cells from the basal layer proliferate, if they still have the power to do so, they do not form normal prickle cell types but are atypical, frequently showing large vacuoles and nuclear fragments. Many dead cells are present and little material is available for the production of the corium which thus thins out and disappears. At this stage a well defined "burn" with a moist, frequently infected surface is present. If sufficient radiation has been given, the skin may be destroyed entirely with the subcutaneous tissues or muscles laid bare. Leucocytes do not as a rule invade the area until the basal layer of cells (de la conche generatrice) (Regaud) has been destroyed and the papillae or rete lost. Probably secondary infection of the surface at this time has much to do with this invasion as most injuries from radiation show little leucocytic reaction. All

stages between the desquamating area of the full blown radiation burn and the normal unaffected skin can be obtained with decreasing amounts of radiation but mild and early changes in the skin are difficult to detect microscopically. The dry, thickened, irregular and roughened, almost senile corium frequently noted after suberythemal doses of radiation, probably is the result of the atypical piling up of dead cells due to the injury in patches of the basal cells of the skin.

Experimental animals have not proven so fruitful in the study of the skin because of the marked differences in thickness, pigmentation, hair distribution, and the frequency of trauma and infection.

Martin (94) using soft radiation on guinea pigs exposed an area 2½ cm. square over the abdomen, giving an erythema dose, so that on the 8th day the skin was brown, by the 10th day an area of desquamation appeared and the hair began to fall out. He studied the changes histologically at various periods. The horny layer was thickened at the end of the 4th day; was quite thick at 6 days; showed some degeneration with desquamation of this layer on the 12th day. The epithelial layer below the horny layer showed enlarged nuclei at the end of 6 days; smoothing out of the rete and sulci; swelling of this layer at the 10th day, and at 12 days the thickness of this layer was two or three times that of the normal and the sulci were lost. Many mitotic figures were present. The hair follicles began to drop out at the end of the 8th day, so that in 12 days there were very few hairs left, with considerable desquamation of epithelium in the follicles. The collagen fibrils or bundles below the epithelium have increased four or five times in thickness. The capillaries between the rete show no changes. The other connective tissue cells show little change. Animals radiated at intervals of two weeks, showed marked ulceration with crusting and shrinking, with sloughing of the surface; destruction of the epithelium of the skin; marked swelling of the collagen fibrils. Desquamation was rather superficial, and rarely complicated by secondary infection. Clark and Sturm (24) were able to show a very sharp border line between simple epilation and persistent alopecia in rabbits with very soft (30 K. V.) radiation.

Hilsnitz (68) was unable to find early changes histologically in the skin of white mice. He used 200 K. V. (hard radiation) and heavy filtration with various amounts of radiation up to seven skin (human) erythema doses. Biopsy material was removed from the mouse at various intervals, usually 24 hours after radiation.

The hair follicle and the sebaceous and sweat gland structures are

sensitive to radiation probably to the same degree as the basal cells of the skin but a slight disturbance in their function or the formation of a few atypical cells has more direct consequences, probably because of their active function. The more passive part played by the basal cells in the gradual production of the horny layer could more readily go on in the presence of considerable damage to cell function without such profound disturbances.

In mice with pigmented hair it has been noted by Murphy (108), using medium wave lengths, that the new hair has lost its pigment. This phenomenon may occur on both sides of the body in these small animals.

A sufficient dose of radiation may bring the process of growth and repair of the matrix cells of the hair to a standstill (141). The hair is loosened and falls out. After several weeks during which atypical cells are present, the growth process starts again, and the matrix cells which have returned to their normal strength and reproductive power proliferate again and produce new hair. As this proliferative stimulus increases, the new hairs form much like the others, though pigment may be absent as shown by Murphy.

Rahm and Koose (125) found that Thiersch skin grafts, when radiated in Ringer's solution outside of the body at 190 K. V., were able to stand as much as two erythema doses without any injury and grew normally when planted. With 3 H. E. D. there was some decrease in size around the periphery. At 4 H. E. D. the skin graft became contracted and did not grow well, so that considerable radiation was necessary to disturb permanently the reproductive power of the skin epithelium.

Thus the primary injury to the skin is one of disturbance to cell reproduction, with either the death and failure in reproduction or the formation of atypical cells, which are able to carry on their normal activity only to the degree to which they are able to return to normal.

The single greatest secondary factor in skin changes following roentgen radiation is the question of cell nutrition as modified by the capillaries. It is the engorgement of the capillaries of the area which produces the erythema noted at various periods after exposure, i.e., three days to five weeks (111), (139), (141–146), (103, 104). The intensity of the erythema and its time of appearance depends upon the amount of radiation given and its wave length. Large amounts of radiation (usually long wave lengths) may bring about an early reaction within one to ten hours (142). Schwarz (143) showed that if one-half of the erythema dose were delayed 24 hours or more, or if it were given in the

presence of a hyperemia, the total effect was less than with the whole dose given at once. In a study of the relationships of time, he found in human skin that if the total quantity remained the same, there was a very much greater skin (capillary) change produced when the dose was given in a short time at a high intensity than when a longer time with a lower intensity was used. In other words, there seems to be a definite increase in the injury quotient with high intensity when using fairly hard radition. Siedamgrotsky (148) studied the effect of roentgen radiation on the capillaries of the skin in first and subsequent irradiations in 53 different types of cases. In a study of the ability of the skin capillaries to constrict and dilate after skin irradiation, he found on the second day, at the time when there was no gross reddening or other reaction observable, that there was a decided hypersensitiveness to adrenalin, with the tendency of the capillaries to constrict greatly increased. The dilatation by means of mustard oil or caffeine was also increased, though not to the same degree. Six days after irradiation, the dilatation of the capillaries with these reagents was about that of normal skin, though constriction under adrenalin still remained abnormal. On the 8th or 9th day, when reddening and the erythema first began, there was a still more marked increase in the constrictive action, while the dilating power was about the same. Capillary changes were still present for a considerable time after an area had been given a single skin erythema dose (or even less), though there was no gross evidence of change to be seen (also Odermatt, 111). There was distinct lessening of the constricting and dilating powers. He concluded that the contractile elements of the capillaries, therefore, had lost their ability to change their state when subjected to a stimulus, because of the changes brought about by radiation. These changes are not thought to be due to injury to the local nervous mechanism. He found that the permeability of the capillary wall was also changed, with at first an increase in permeability followed by a decrease, from a primary injury to the endothelial cells. David (33–35) after six years study of various types of cases with the capillary microscope, came to the conclusion that the contractile elements of the capillary wall showed some of the first effects of the roentgen rays, though there are individual differences, and functional disturbances are frequently seen without anatomical changes being apparent. In many late injuries after roentgen radiation, these injured cells do not repair well or grow well. He points out that very often without any apparent anatomical injury, the capillaries show very marked functional changes brought about by the radiation.

Amitotic nuclear divisions in the dermal tissues, the epithelium, sweat glands and endothelium of the blood vessels were described by Schreus (140). The amitosis may occur in the epithelium without the skin showing visible reddening, and there is still some question whether there is a direct relationship between the nuclear divisions and the waves of erythema. With relatively hard rays and either with or without filtration, the radiation through very small portals does not produce an erythema, due to the fact probably that there is no participation of adjacent tissues in the general reaction of the capillaries of the skin so that the presence of increase in circulation could not be identified, visibly. He confirmed the observations of Miescher (105) who observed successive waves of erythema. The first erythemal wave occurred one to four days after radiation; the second, often the strongest, between eight and twenty-two days; the third between thirty-four and fifty-one days. Occasionally a fourth wave of erythema was noticed on the sixtieth day. There is a certain level of dosage which gives a maximal erythema and any increase in the amount over this produces no greater erythema, even though the separate stages may be run together indistinguishably and the injury to the skin progress to a "burn," dermatitis or an ulceration.

Lazerew and Lazerewa (86) investigated the pharmacological and pharmacodynamic effect of various alkaloids upon the blood vessels and capillaries of the excised rabbit's ear. Different lengths of time varying from 5 minutes to 2 months after the radiation of one ear, the rabbit was killed and both ears removed and the circulation rate of perfused fluid through the ears determined. They report quite consistent results. The blood vessels in the radiated portion of the ear were dilated much more than on the control side because the flow of the fluid was considerably greater. The effect of various pharmacological substances upon the isolated ears was somewhat greater on the radiated side, where also the fluid flow was markedly greater, and perhaps the reaction was intensified because of this. Even small doses of radiation brought about moderate changes which were present for several weeks. The very largest doses with erythema and epilation produced changes which persisted for two months. During the period of the erythema the widening of the stream bed was very great, due to disturbances in the blood vessel regulating mechanism. These authors have reviewed the subject at great length.

Wynen (164) found that hyperemia of the human skin by means of diathermy applied before and during radiation, required 30 to 40 per

cent less radiation than that needed to produce an erythema on the unhyperemic skin or the skin before diathermy was used. The skin, when a combination of hyperemia and radiation had been used, showed a very marked influx of edema, which seemed to be due to the injury of the blood vessel walls. These had been changed perhaps by the unusual elevation of the temperature or through some other mechanism, such as changes brought about by the high frequency currents.

Using 170 kilovolts and a moderate amount of filtration, following sympathectomy of the femoral artery of a dog, Wynen found that the hair fell off and an ulcer was formed about 1 or 2 days before the changes appeared on the control side. After the complete occlusion of the vein over a length of 4 cm. in one leg in a white dog, following which both legs were radiated, if just the right amount of radiation was used, a small amount of epilation appeared in 60 days on the side where the occlusion of the vein had been done. On the control side, various stages of epilation developed, but in 80 days the hair had come back. In 120 days, on the abnormal side, the hair had come back and the skin was intact, but on the control side there was no hair and the skin was thin and dry. Following the occlusion of some of the large arteries of the leg, no difference in the control and ligated leg could be detected from the radiation. Apparently radiation seems to cause the greatest amount of injury to the blood vessels when the vessels are dilated and the blood is flowing through them rapidly. This is demonstrated by the contrast between hyperemia and venous stasis, where the injury is much less. Although the blood vessels may be dilated perhaps to the same extent, the blood flow is much less rapid. Irritative agents such as croton oil (65), ultraviolet light (119) administered at the time of the radiation are known to intensify the reaction.

So far only acute changes in the skin have been considered. Chronic changes may be manifested by excessive pigmentation and keratosis, irregular areas of depigmentation, indolent shallow ulcers, healing of repeated indolent infections, telangiectases, and severe pain. Wolbach (162) has described changes in the skin epithelium, in lesions obtained from the hands of roentgenologists in which all stages of degeneration of the epithelial cells were present—vacuolation, pycknosis, desquamation of the horny layer, shallow ulceration with loss of the epithelium and only a feeble reparative process at the margins of the defect. Either loss of the rete may occur or an irregular thickening with downgrowth and proliferation of the basal cells with occasional pearl formation to all intents suggesting malignant change. Although malignant change

has developed all too frequently in roentgenologists and occasionally in severe roentgen ray burns, it has been difficult to produce it, experimentally, probably because of the time element necessary. Bloch (12) developed a metastasizing tumor on the ears of two rabbits after 22 and 32 months of repeated radiations. Goebel and Gerard (58) were able to produce only one tumor after repeated exposure of 21 guinea pigs to radiation for 15 months. This tumor was sarcoma-like.

Disturbance of nutrition seems to be a marked factor in the chronicity of this type of lesion and most authors agree that the capillaries show distinct changes with a tendency to complete obliteration. This seems to be mainly, if not entirely, due to changes in the connective tissue elements both in the walls of the capillaries and in the nearby subcutaneous tissues. There is pretty general agreement that moderate changes such as swelling and frequent mitotic figures are to be noted in the connective tissue cells following large amounts of radiation about the time the erythema develops. Wolbach (162) and others (54, 127) have described chronic indolent changes in the connective tissue cells of the subcutaneous tissues. Fibroblasts are atypical. Repair is slow. "Fibrosis" with contracture and shrinking of the fibroblastic cells in the subcutaneous tissues and the walls of the capillaries is widespread. Thrombophlebitis is a frequent occurrence, perhaps because of the obliteration of the lumen by the shrinking of the injured connective tissues in the capillary walls or from primary injury to the blood vessel endothelium.

Lieber (89), by microchemical methods of Macallum, studied the distribution of calcium and potassium in the skin of white rats, guinea pigs and dogs. The latter were unsatisfactory, due to the large amount of fat present. Microchemically in the controls there was an accumulation of potassium in the hair follicles and in the depths of the epidermis. Following irradiation, the potassium in the vicinity of the hair follicles practically disappeared, and the zone in the epidermis became broader, irregular, and very diffuse. In another series of sections in the same animal, the calcium in the normal skin was shown as a mesh or net-like structure throughout the skin, with the hair follicles and especially the hair roots practically devoid of calcium. The epidermis showed no calcium. Following radiation, the normal distribution of the calcium was distinctly destroyed and it was collected in the neighborhood of the follicles and the epidermis. The disturbance in the physical-chemical equilibrium of these ions may cause considerable functional disturbance in the tissues.

As the rôle played by injury to the connective tissue is little understood, the experiments of Maximow (102) and Strangeways (152) are of great interest. Maximow (102) examined the connective tissue cells around a piece of celloidin block at various intervals, after exposure to soft radiation, and found that the young, rapidly growing and dividing fibroblasts were prevented from dividing or divided atypically. Marked increase in size and loss of the power to form collagen fibrils occurred. Edema developed in the older connective tissue near by the inflamed area and clotted fibrin appeared. The fibroblasts, with the large nuclei and large amount of protoplasm seemed incapable of recovering from their injury for a long time (i.e., up to 27 days) though in 2 months there was little difference from the control. Old connective tissue cells in the form of a scar he found unchanged by the radiation. The endothelium of the capillaries became swollen and their nuclei fragmented.

Strangeways and Oakley (152) radiated cultures of connective tissue from the choroid of the chick's embryo with very long wave lengths for varying intervals. In cells radiated during the resting period, enlargement of the nucleus and cytoplasm was noticed, with granular changes in the cytoplasm, and the appearance of deeply stained chromatin particles in the nucleus, especially after the prolonged exposures. Disintegration of the chromatin may be gradual or more or less explosive. Small amounts of radiation caused granular changes in the chromosomes in various stages of the mitosis. Somewhat larger amounts brought about a lag in the division rate, with a tendency to disintegration or disappearance of a stage of the mitotic process with fragmentation of the chromosomes. No changes were discernible with very small amounts of radiation. Very large amounts of radiation caused clumping or agglutination of the chromosomes in the cells at the metaphase with disintegration later on without the mitosis being completed. Incubation of the cultures after radiation indicated that there was a latent period of 15 to 20 minutes before changes in the cells could be recognized. Ewing (54) thought, from the study of tumors which have been radiated, that injury to connective tissue by radiation caused inflammatory injury with resultant proliferation of fibroblasts and repair with fibrosis.

These experiments would indicate that actively growing fibroblasts are relatively sensitive to radiation. Autolysis experiments in (157) dogs indicated that the adult connective tissue and blood vessel endothelial cells were two of the most resistant cells in the tissues to autolysis,

both before and after radiation. In the autolysis experiments the organs were autolyzed at periods varying from 2 hours up to 4 days after exposure to radiation, and no difference detected in the reaction of these two cell types, although profound changes were evident in other cells.

The next major consideration is the change produced by various types and amounts of radiation, in the blood—its cellular components, both in the circulating medium and the bone marrow, and the chemical constituents of the serum. The production of a leukopenia is well known and has been recently reviewed by Spurling and Minot (150) and Kolta (79). Murphy (109) has shown the extreme sensitivity of the lymphocyte and has been able, by suitable dosage, to deplete the lymphoid tissues (1926) in laboratory animals without causing appreciable changes in the rest of its body function, and still allowing the polynuclears to remain relatively unchanged in numbers. The lymphocytes were at their lowest level about 48 hours after the last "x-ray treatment." Their recovery was slow and depended somewhat upon the dosage used, for with large doses they did not return to the original number for one to two months. Very small doses of long wave lengths of radiation brought about a definite increase in the number of the circulating lymphocytes in normal mice. Murphy (109) thought this a definite response to mild injury of the lymphoid system. Serum from rats recently radiated with moderate amounts of long wave lengths was able to increase the number of suspended lymphocytes following incubation and protected them from disintegration, so that at the end of 24 hours' incubation, the suspensions of lymphocytes in serum from the radiated rats contained much greater numbers than the controls. In vitro radiation of the serum caused no such changes. As the number of experiments was large and the work well done, the evidence which Murphy presents in favor of a stimulative action on the part of small doses of "soft" rays must be seriously considered. This is the first real evidence presented which suggests a true stimulative action by small doses of radiation. Murphy has summarized the work done on the lymphocytes in a recent monograph, where the reader may find complete references and tables. Lenz (87) was unable to increase the size of the thymus of young rabbits by the application of from one-fortieth to one-fifth of an erythema dose. Falconer, Morris and Ruggles (55) using radiation, the amount and type of which is not stated, over the long bones of the dog, were unable to demonstrate either stimulation or increase in the bone marrow cells. Radiation over the spleen in small

doses caused a slight increase in the number of cells in the bone marrow, and a slight increase in the red blood cells. They found also a rise in the number of circulating platelets. Lacassagne et al. (84) thought that the red blood building apparatus was injured much like that of the leukocytes by radiation. Herzog (67) influenced by the rather favorable results published by Bucky and Manheimer, who suggested that stimulating doses of radiation over the erythropoietic system caused an improvement in blood regeneration, performed experiments on guinea pigs, using 125 K. V. with direct radiation of the bones. This caused a primary injury to the blood forming elements. A small general radiation caused a drop in blood formation at first, but later was followed by an acceleration in the regeneration, which overcompensated quickly for the original loss, with the result that there was an increased output of the blood elements. In one experiment with unfiltered radiation over the whole animal, the result was much like that obtained by protein shock, with an acceleration of production of blood elements for a short while. He was convinced that direct radiation destroyed or inhibited the blood forming elements, though small amounts of radiation would probably affect regeneration and act as a secondary stimulus because of the overcompensation to the injury. Murphy (109) found no changes in the bone marrow in those animals responding to the radiation by an increase in the number of circulating lymphocytes.

Kromeke (82) in a very thorough study of the effects of roentgen rays on the red blood cells and plasma, exposed rabbits to heavily filtered high voltage radiation and did blood studies on the rabbit before and after the radiation. Nine out of ten animals showed plainly a polycythemia, sometimes as high an increase as 28 per cent. There did not seem to be any relationship between the amounts of radiation given from 1 to 20 H. E. D. Two of the animals died after 37 days, with a progressive anemia. In all of the animals there was a latent period of from 3 to 5 days before any change in the red blood count could be noted. In five out of seven rabbits, the highest count was reached on the eighth day, when there was an increase from 4,700,000 up to 6,030,000; an increase of about a million. The hemoglobin kept parallel to the red count. The refractive index of the serum proteins usually decreased. There was usually a leukopenia which was more or less transitory. The body weight in these animals remained practically constant, though by inspection of the tables, 100 to 150 grams were shown to have been lost in three to four days. The changes in the red count did not seem to be due to dehydration, because the dry residue of the blood remained

the same or decreased slightly, and the refractive index readings of the serum protein or albumin paralleled this, showing an apparent increase in the water content for the 24 hours after the radiation. This decreased somewhat later. Nucleated red cells were not seen, nor were eosinophilic or basophylic cells ever seen in the smears of the blood. There was a normal count of polychromatophilic cells. He was unable to produce a hemolysis of the red cells by any amount of radiation in vivo. Doornkaat (45) was unable to produce hemolysis in vitro with heavily filtered radiation up to 1½ H. E. D. Holthusen (69) was able to produce hemolysis and the production of methemoglobin in the circulating blood with 50 H. E. D. Using sodium sulphate solution, as a test of the fragility of radiated and non-radiated cells, Krometke was unable to show any difference in the hemolysis curve 48 hours and 72 hours after radiation of the rabbits. An examination of the bone marrow of several animals before and after radiation did not show any difference in the erythropoietic cells. He also pointed out that there was considerable variation from animal to animal in both the normal and the radiated rabbits. After a very complete and thorough review of the literature on the subject, and his own data, Krometke came to the conclusion that the very rapid erythrocytosis immediately after radiation is not due to new cell building, but to a throwing into the circulating blood of reserves from the peripheral circulation.

Forty days after doses of 2 H. E. D. (Krometke), the radiated and unradiated bone marrow showed an increase in the number of erythrocytic elements, with an increase in the general count of the erythroblasts and the number of young or old nucleated forms. In the larger and very largest doses, after 12 days, and up to that of 40 days, there is a very marked difference between the radiated and unradiated bone marrow of the vertebrae, in that the myeloid elements had decreased considerably on the radiated side, but were still present on the unradiated side. The erythropoietic cells were very markedly decreased in the unradiated bone marrow, where a greater number of young erythroblasts were found than in the normal. The unradiated femur marrow was changed from a normal fatty marrow into an erythroblastic marrow.

Since the bone marrow had been greatly injured and relatively young cells are being thrown out, the color index necessarily dropped. In several of the rabbits there was a variation in size and shape, with occasional polychromatophilia and a few normoblasts in the circulating red blood cells, 30 days or more after the radiation. Apparently the bone marrow had used up its reserve and was making new cells. This

would account for the drop in the hemoglobin and color index. He concluded (confirmed by Doornkaat, 45), that radiation causes an injurious effect upon the erythrocytic apparatus, in which small and middle sized doses are followed by increased regeneration and repair, but large doses were not followed by repair. There is a very large bibliography attached to this article.

Kolta (79) and others, using moderate doses of radiation in patients, have found no demonstrable change in the hemoglobin or red blood count. Lacassague (84) likewise demonstrated no change in rabbits and guinea pigs. Pohle (120) studied the sedimentation rate of erythrocytes in vitro and in vivo in normal individuals who had not previously had roentgen ray treatment. He thought that there was a certain minimum dose (at 135 K. V.) which was required to cause a delay in the sedimentation velocity of the red blood cells. This was thought to be a reversible reaction, but bore no definite quantitative proportion to the amount of radiation received. Cordua (28) was unable to demonstrate in a large number of cancer and other types of patients, any change in the sedimentation rate of the red blood cells or the viscosity of the blood serum. Jaller (77) found no change in the sedimentation rate of red blood cells radiated in vitro. Brummer (16) thought that very large amounts of radiation administered to defibrinated blood in vitro, caused the red blood cells to sediment out very much faster than the controls, but had very little effect upon washed corpuscles. Bonanno (13), in a general review of the work done on sedimentation rate of erythrocytes as affected by radiation, studied 30 cases before, during and immediately after and several hours after radiation, and found no changes which could not be explained on other factors generally inherent in the disease itself, and these effects, when present, usually lasted only a few hours. They were most common in cases where vascular regions or the abdomen were radiated, and he thought this increase in sedimentation rate was dependent upon an increase in fibrinogen (which was increased). Pagniez, Ravina and Soloman (116) found that radiation of most any portion of the body would shorten the coagulation time of the blood. It was not necessary to radiate the spleen for this purpose. Four to seven days after radiation, the coagulation time usually returned to normal. In vitro radiation of blood has no effect whatever on coagulation, even in very large amounts. Apparently radiation of moderately short wave lengths was used. Kolodny (78) and Kolta (79) found similar changes in rabbits.

The acute intoxication frequently seen following exposure of the

body, most commonly the abdomen, has been a constant source of controversy. When a large volume of cells have been injured and destroyed, as when the intestine is radiated, the resulting intoxication would reasonably seem to be a result of this cell disintegration. This should be clear when many workers (Martin, Whipple, Cori, etc.) have shown coincident changes in the normal blood and urinary constituents. Whipple (157, 158) et al., showed that the maximum disintegration of the intestinal crypt cells paralleled the evidence of the intoxication at its peak.

A discussion of the changes in the chemical constituents of the blood is very difficult because there is often no correlation between dosage, wave length and organ or region radiated. For this reason a large amount of detail is necessary and the reader is left to draw his own conclusions.

There seems to be considerable difference in the findings of various authors in the cholesterol content of the blood following radiation. With high voltage, Konrich and Scheller (80), in the healthy rabbit, were unable to show any definite change in the blood cholesterol. Roffo and Correa (131, 132) showed both in patients and in white rats with tumors, if the tumor were shielded and the body radiated there was a very slight increase in the cholesterol. If, however, the tumor were radiated there was a distinct drop in the cholesterol content lasting twenty-four hours or longer. Smyth and Whipple (149) found that radiation over the liver of bile fistulae dogs caused a depression of the bile salt output which was prompt or delayed to the second day. Fairly large doses of radiation were necessary, as small amounts produced no change. They predicated a moderate grade of liver cell injury by the radiation which was much less than that done to the organ by chloroform or proteose poisoning. Babarczy (4), using heavily filtered high voltage radiation on bile fistulae dogs with a fair amount of radiation showed a marked increase in the twenty-four hour output of bile, following radiation of the liver, with much darker color and a fourfold increase in the biliary cholesterol without any definite change in the blood cholesterol. Several days later the quantity, color, and cholesterol content of the gall gladder bile returned to the original value. As soon as the cholesterol content of bile had returned to normal, the level of blood cholesterol doubled; then finally returned to normal. Levy-Dorn and Burgheim (88) thought that they were able to show a very great fall in the cholesterol content of the blood in a healthy dog and patients without malignant disease, while radiation of carcinomata

or sarcomata in other patients brought about increase in the blood cholesterol.

The blood sugar metabolism seems to vary considerably both because of the region radiated, the amount of radiation given and the species studied. Kolta (79) found an increase in 10 patients in the blood sugar between one-half hour and 24 hours after radiation, returning to normal two days later. Strauss (151) pointed out that at first the blood sugar content varied with the animal used and it was markedly increased in the rabbit, as consistently shown by many workers (154), and decreased immediately after radiation with rapid return to normal in the dog. In the rabbit radiation of pancreas and liver caused an increase in the blood sugar. In dogs complete removal of the pancreas followed by radiation caused a very marked accentuation of the expected blood sugar increase. Radiation of the isolated adrenal in dogs caused a drop in the blood sugar level after a period of several days. Strauss came to the conclusion that the adrenals are not very sensitive to radiation in so far as their physiological effects were concerned.

Although the results on the blood sugar and the blood cholesterol vary considerably, the cholesterol content seems to bear some direct relationship to the destructive effect of radiation upon body cells and to a direct effect upon the liver when that organ is in the field of radiation. The blood sugar seems to be concerned with the function of the liver or the pancreas which is very frequently within the field of radiation, when the liver is exposed.

There is a rather general agreement (29, 30, 79) in the response of the blood chloride which is considerably decreased while the excretion of urinary chloride is increased. Cameron and McMillan (19) found that patients after massive doses of radiation therapy had a reduced urinary output with moderate sodium chloride retention. Kroetz (81) found a uniform response in this regard in that there was an increase in the sodium content of the tissue juices and a decrease in the chlorine content. This relationship was bound up with the alkalosis and changes in pH in both man and dogs. There is an immediate, very temporary anoxemia followed by an alkalosis, lasting for several days (29, 30, 47, 48, 79, 81). Kroetz (81) found in man during the first hour, a fall of from three to ten volumes per cent of the serum bicarbonate and a considerable rise in the pH, with a considerable increase in the carbon dioxide capacity the following day and a return to normal of the pH,—a return to normal or a slight drop in the pH, which may persist for several days. These changes were quite small but constant. The alkalosis of

the blood after radiation was first described by Hussey (72) in rabbits. The early anoxemia within the first day was confirmed by Lapatsanis (85) on many patients. Pannewitz, (117, 118) on rabbits and human beings, found a transitory (2 to 5 hours) acidosis immediately after radiation.

Schneider (137, 138) using paramecia, found that these organisms when placed in an alkaline electrolyte were killed more readily by radiation, and thought that the death of the cells was bound up with electrolyte and the relative alkalosis. Pagniez, Ravina and Soloman (115, 116) in 30 patients in which various portions of the body were radiated, found a definite alkalosis one hour after radiation, in $\frac{3}{4}$ of the number, and that no definite localization of the area radiated seemed to be necessary.

Tsukamato (154), using the rabbit, radiated the liver with heavily filtered radiation and apparently obtained atrophy, with increase in the rest nitrogen, amino acids and urea contents of the blood, this within 24 hours after radiation in the fasting animal, and a gradual increase in these elements was noted, with emaciation of the animal and death in 14 days. No mention is made of lesions of the intestines or injury elsewhere. Doub, Bollinger and Hartman (47, 48), using 200 K. V. and heavy filtration, with dosage unstated, showed in a series of experiments on dogs and from observations of patients receiving therapy, that there is a distinct rise in the acid soluble phosphorus in dogs after radiation, with a return to normal on the second day; with a fall in the water soluble and inorganic phosphates with corresponding increases later. These changes were not quite so striking in patients. The carbon dioxide combining power showed no distinct change, yet there is a distinct alkalosis beginning early and lasting over a considerable time, depending upon the amount of tissue radiated and the dose. In large lethal doses, the alkalosis persists for days; with smaller doses there is return to normal within 24 hours, with over-compensation. In dogs there is quite a sharp and consistent rise in the sugar curve immediately after radiation, with a fall and secondary rise on the third day, though in some animals the changes are not very striking. The changes are greatly increased by morphine and ether. The amino acids of the blood are markedly decreased during the first 24 hours, and after that remain about the same. In the dogs, the non-protein nitrogen shows a marked decrease in the first few hours, with later increases of 75 to 100 mgm. per 100 ccm., especially in the fatal experiments. There is a very slight decrease in the calcium content of the blood serum.

There is considerable evidence of change in the urinary constituents following the treatment of patients with tumors and various other diseases where large amounts of cellular material are destroyed (29, 30, 42, 43). Cori (29, 30) found the total nitrogen excretion increased after radiation, usually proportionate to the decrease in the size of the tumor. The urea, ammonia, uric acid and phosphorus excretion was increased. The chlorides were retained in the body. In experiments on animals and in patients Dodds (42, 43) found a sudden fall in the 24 hourly amount of urea, uric acid, ammonia, creatinine, inorganic phosphates and the acidity, with a decreased volume output of the urine lasting for several days with the return to a normal figure in three days. There is a slight increase in the uric acid and phosphates beyond the normal level for five days. There is a marked increase in the chloride output after radiation with normal level in from three to five days. These changes were not present when radiation occurred over the head and chest, but were accentuated when the radiation was given over the abdomen or the spleen in the case of the leukemia. Buckman (17), in leukemia and carcinoma cases using deep therapy, showed a very marked increase in the blood and urine phosphorus immediately after the radiation with a return later to a normal level without any change in the inorganic phosphorus during the period in which the white blood count dropped and there was considerable destruction of tissue. Cori (29, 30), Martin (96, 97), Warren and Whipple (157, 158) and others agree that there is considerable increase in the output of urinary nitrogen when dogs are radiated over the abdomen with symptoms of intoxication. It should be pointed out that there is considerable variation in all of these results because distinctly abnormal individuals were used and because of the variation in the site of radiation in experimental animals, the species used, and the amount of injury produced.

Ludin (91, 92) exposed ten guinea pigs and two rabbits over the liver region to soft radiation in large amounts. Those receiving unfiltered radiation daily died in 5 to 7 days with no demonstrable changes in the liver except hyperemia and cloudy swelling. With moderate filtration, the animals lived longer and were less intoxicated and there were some changes in the liver cells which showed chromatin damage and some fat droplets. There was no mention of lesions elsewhere which might have explained the intoxication and death of these animals. He and others (15, 157) do not think that the liver is very sensitive to radiation. Ludin (92), using rather large amounts of soft radiation, over the uncovered back of the rabbit, centered over the liver region, found a rise in the

blood sugar volume the first 15 minutes following radiation in animals which had been radiated 14 hours after the last feeding, and remaining on a basal metabolic rate. The blood sugar then decreased rapidly for several hours, so that after 22 hours, the value was about normal. In rabbits starved for two days, radiation caused no increase in the blood sugar, but a distinct drop for 4 hours after treatment. There is no proof that these blood findings are due to effects of radiation upon the liver. Kolodny (78) using 200 K. V. and heavy filtration, using about 2 erythema doses, exposed the whole body of a rabbit. These animals died from the third to the ninth day. He studied the liver particularly, and saw small focal areas of necrosis, with the presence of some round cells and considerable phagocytized material. Gabriel (56), using 200 K. V., was unable to find liver changes. Tsuzuki (155) reported degeneration of the liver of rabbits with later atrophy following the use of 170 K. V. radiation. Other workers (95, 96, 157, 158) do not report injuries to the liver of dogs with medium wave length radiation. Patients with malignant disease radiated over the liver with deep therapy are reported by Case and Warthin (22) as showing marked fibrosis of the liver. Direct irradiation of the region of the liver or pancreas may cause profound changes, yet these organs are not readily radiated in place, and the status of liver injury by radiation is still in controversy.

Orndoff, Farrel and Ivy (113) isolated the tail of the pancreas under the mammary gland in six dogs, and after sufficient control examinations, radiated the transplanted pancreas with full protection of the rest of the body and the abomen, using heavily filtered radiation at 150 kilo volts. They varied the amount from 1/10th to one erythema dose in different dogs. With 1/10th of a human erythema dose, the secretions did not change in quantity for 20 days after the exposure. The lipase content was slightly increased, and the trypsin was definitely increased. One-half of an erythema dose caused an increase in the quantity of the secretions during the first 14 day period after the exposure. Two of the animals were secreting more juice than normal, 46 and 38 days after exposure, but the other one at 27 days was secreting less than normal. The lipase concentration was not changed during the first two weeks. At 41 and 37 days respectively, two dogs still showed an increase in quantity. The lipase was definitely increased, while in the animal showing a decrease in quantity, the lipase was normal. The trypsin in one animal remained the same, while in the second animal, it was decreased for six days and then returned to normal. In the third

animal it remained normal for 14 days, and then definitely increased, but as the total quantity was decreased the quantity of trypsin probably approximated the normal. One erythema dose caused a definite decrease in the quantity in both animals, with apparently a return to normal in one dog in 47 days. The lipase concentration was not materially changed, while the trypsin definitely increased 14 days after exposure. In the other animal there was slight increase, though this may again be accounted for by the slight decrease in the secretion.

They point out that the reaction of the pancreas, especially in regard to their own experiment, is quite variable in its response to roentgen rays, and that the regenerative power is very great. They are not quite ready to state that roentgen rays directly stimulate the gland. They point out that other experiments are necessary to further prove their point in regard to the change in enzyme concentration, volume output, etc.

Salis (134) did not think permanent injury to the salivary glands was produced by radiation, even though degeneration and atrophy of the secretory elements could be demonstrated. Case and Boldyreff (21) found a decrease in the saliva output in dogs, to one-fourth the normal amount, after radiation of the parotid gland with short wave lengths. There was a gradual increase with return to normal in one month.

The gastro-intestinal tract is quite sensitive to radiation. Regaud et al. (129) using a gas tube and soft radiation demonstrated destructive and atrophic lesions of the mucosa of the stomach and small intestines. Warren and Whipple (158) and Wolfer (161) produced chronic indolent ulcerative lesions in the stomach using medium wave lengths of radiation. Ivy (75) and Dawson (36) saw changes in the chief cells with pycknosis, atrophy and autolysis and disappearance of these cells with only parietal and mucus cells remaining in the frame work. Dawson studied histologically the changes in Pawlow pouches in dogs exposed to large doses of short wave lengths, sacrificed at the time when hypochlorhydria or, in later stages, an achlorhydria was present. A definite injury occurred mainly to the mucus and neck and chief cells. The chief cells have undergone cytolysis while the parietal cells were more resistant. The persisting parietal cells showed no histological evidence of injury, yet they were unable to produce acid. The mucosa showed passive hyperemia, without infiltration of white cells or fibroblasts or phagocytes. Necrotic tissue was sloughed with very slow indolent regeneration, from the deeper cells. There was a reduction in thickness when healing occurred, but apparently otherwise the mucosa was normal

in appearance and function. The functional studies of gastric acidity and ferment content showed considerable variation. Miescher (104) using Pawlow pouches in dogs, found that exposure over the stomach would decrease the acid, though the other gastric contents might be increased, especially the pepsin. This started on the third day, reached its maximum on the tenth day, and returned to normal in about 2½ months. Doses of equal intensity given at three weekly intervals, gave a complete suppression of gastric secretion, which rapidly returned following the cessation of treatment. With a low hydrochloric acid content the pepsin was rather high. Ivy and his co-workers (74, 75), using 110 K. V. over the stomach, showed marked hyposecretion in the cardia, with reduction in the pepsin content. The acid secreting power of the stomach was more sensitive to radiation than the sources of the ferment. Three or four weeks after the radiation, the gastric juice returned to normal acidity, but it was permanently reduced in quantity. Bensaude, Solomon and Oury (10) radiated the abdomen over the stomach in both man and animals, using 120 kilovolts, giving suberythemal doses one or two times a week with the production of an erythema about the 8th to 12th treatment. In a third of the cases there was a quick drop in the gastric acidity during the first hour after radiation, which was of a transitory nature and returned to the previous acidity the next day. The rest of the cases were not modified by the single or first dose. After several doses of radiation, 55 per cent of the cases showed a rapid drop in the acidity; 25 per cent, a slight drop; 20 per cent, no change. The experiments were not carried on long enough to note whether a gradual decrease in the amounts was produced, and no more ascertained than the immediate effects.

Portis and Ahrens (123) using Pawlow's pouch on dogs, found that when the radiation (200 kilovolts) was given over the thorax, practically little or no effect was obtained. With the same exposure over the abdomen, the gastric secretion and acidity were markedly lowered. Examination of their daily curves over a period of several months shows quite marked daily variation in both the free hydrochloric and the total acidity in both normal and post-radiation periods, so that slight changes in acidity are of no consequence.

Dieterich and Rost (41), using two dogs, with rather hard radiation, gave from 41 to 206 per cent of the erythema dose over various portions of the body of these animals, which had gastric and duodenal fistulae. They were unable to find any changes, nor were they able to produce any reduction in the acid or enzyme values when direct radiation over

the stomach was performed. Their experiments are too few, yet constant over a long period of time.

The acute injury to the mucosa of the small intestine by medium wave lengths was extensively studied by Whipple and his co-workers (61, 157, 158). It was noted that a rather definite amount of radiation of medium wave length over the abdomen of dogs, cats, rabbits and general exposure of guinea pigs, rats and mice caused rapid intoxication and death on about the 4th day. This had been described before (129) but they were able to localize the cause for this in the widespread destruction of the mucosa of the small intestine. Radiation of the thorax of a dog with similar or larger doses, with the abdomen shielded, caused only the commonly observed fall in leukocytes, and a transitory and slight rise in the urinary excretion of amino nitrogen. There were no observable clinical symptoms of intoxication from radiation of the thorax (123, 157, 158).

On studying the intestinal mucosa at intervals (158) up to the day of exitus, in those animals radiated over the abdomen, it was found that the crypt cells of the entire small intestine from the pylorus to the ileocecal valve were mainly involved in this injury. Changes in the chromatin of the nucleus of the crypt cells of the small intestines could be seen two hours after the exposure to the radiation. Cell damage was marked at 24 hours and disintegration began at 48 hours and was extensive by 72 hours. Coincident with the beginning of the disintegration of these cells clinical symptoms of intoxication were first manifested and by 72 hours the animal was nauseated, refused food and had a diarrhea. On the 4th day the mucosa of the dog's small intestine had practically sloughed away from the muscularis mucosa. The animal was rapidly becoming dehydrated from the voluminous, watery, black, almost tarry diarrhea. The urinary nitrogen output had almost quadrupled. There was destruction of the lymphoid cells in the lymph nodes and spleen but little other evidence of injury except for the intestinal lesions to account for the profound intoxication and death of the animal. Similar lesions were found in the intestinal tract of the other laboratory animals except birds, snakes and frogs. Kolodny (78) and Tsuzuki (155) also observed intestinal injury in rabbits by radiation of short wave lengths.

The minimal amount of radiation necessary to cause death of the animal (157) was quite definite and in comparison with other biological units, an amount resembling a minimal lethal dose seemed to be established, which was quite constant for each type of laboratory animal used. Survival with the production of chronic lesions resulted when

less than the minimal lethal dose was used, unless intercurrent infection intervened. The symptoms of intoxication were correspondingly less as the dosage was reduced. Any increase in the dosage over the minimum lethal dose did not change the symptoms any nor did it hasten the progress to exitus, although there was evidence of destruction of more cells from the larger dose. There seems to be, therefore, a definite time element or latent period for the very sensitive crypt epithelial cells of the small intestine to undergo destruction just as there is for the gonads, skin, etc. (127). Also there seems to be produced by the destruction of these cells in such quantity by radiation, a definite toxic substance or substances which cause death when elaborated in sufficient amounts. The nature of this substance can only be speculated upon.

The description of chronic ulcerative indolent lesions in the intestinal tract was first made by Regaud et al. (129) using gas tubes. Similar lesions were produced with both long and medium wave lengths by Martin et al. (96, 97) and Whipple et al. (158) in dogs. There was usually some intoxication and diarrhea, which soon cleared up. Later on symptoms of cachexia developed with exitus at various periods, usually dependent upon the amount of intestine left intact. Whipple et al. (158) showed that these lesions were sharply circumscribed and that there was little evidence of scattering beyond the primary beam even deep within the abdomen. There was little difference between the sharpness of the edges in the lesions produced in the small bowel whether it was radiated in place with medium wave lengths (158) or a loop exposed upon the abdomen to unfiltered radiation of (soft) long wave lengths (96, 97). Both Mottram (106) and Martin (96, 97) observed failure in the filling of the lymphatics with fat in the mesentery of loops of small intestine which had received radiation a week or more previously.

Chronic ulcerations in the intestine of patients have been all too frequently found after therapy (160). Two reports recently are unusual in the extent of the lesions and their correspondence to the experimental findings in animals just discussed. Sanders (135) reported a case of intestinal injury 6 months after radiation of the lower abdomen with apparently normal dosage. Macroscopically there were two extensive penetrating ulcers of the intestinal wall. Microscopic examination of these regions showed generalized breaking down and destruction of the epithelium, with abnormal nuclei. The main degenerative changes were found in the blood vessels with endarteritis and endophlebitis obliterans, which also could be seen to be present in otherwise unaltered regions. There was some damage to the local nervous plexus

as well. There was a pronounced connective tissue proliferation in the submucosa, with active capillary formation. There were many plasma-cells and new fibroblasts and active mitoses. Evidently, then, if a long enough period of time had elapsed with the person surviving, chronic changes in the blood vessels may occur much like those in the skin. Ball (1925) described a patient radiated over the abdomen for carcinoma of the cervix with large amounts of deep therapy. She was ill for several days with diarrhea and a general intoxication. She died in 38 days with progressive cachexia, frequent bloody stools. Autopsy showed atrophy and degeneration of the abdominal muscles, ulcerations throughout the small intestine with areas of semi-gangrene for about twenty-four inches of the intestine.

Injury to the kidney is rather difficult to demonstrate because of the frequency with which nephritis occurs spontaneously in laboratory animals. Using medium wave lengths McQuarrie and Whipple (93) were able to show moderate changes in the urea output and the renal function with but little structural change, following radiation of the kidney region of adult dogs with tremendous amounts of radiation.

Gabriel (56) in his review of the literature, pointed out a great many discrepancies of the effect of radiation upon the kidneys, with various types of radiation. In a perfusion experiment with the excised rabbit's kidney he demonstrated a depression of the flow of the fluid for a small period of time after radiation, which he thought was due to a contraction of the blood vessels from the radiation. This was much less with the unfiltered radiation and greatest with the more heavily filtered radiation at 200 K. V. Using cats, rabbits and dogs, he radiated the kidney areas both bilaterally and singly, giving a large amount divided up into different intervals and waited until the animals died. He found considerable difference in the kidneys of the different species, but in general the blood vessels were dilated for short periods after radiation. This was true throughout the kidney structure and also in the glomeruli. Occasionally there was bleeding and hemorrhage around the glomeruli and some swelling and changes in the nuclei of the epithelium of the tubules. Occasionally the glomeruli structures were entirely destroyed and replaced by necrotic material and hemosiderin. The tubule cells were markedly swollen, showed necrosis and fat globules. The changes were not so marked in those cases receiving smaller doses over long periods of time, but they showed some shrinking of the glomeruli, with bleeding in between the cells and beginning connective tissue reaction. The cat which had been radiated for over a period of six months, showed

shrinking of the kidney to one-third of the size of the control with compensatory hypertrophy of the control on the unradiated side. There was a great deal of hyalin degeneration of the glomeruli and other parts of the kidney parenchyma and a great deal of connective tissue reaction around the blood vessels and interstitial tissues. Such great changes were not obtained in the rabbit kidneys. In dogs, several months after rather marked amounts of radiation, there was cloudiness of the urine, with later the appearance of albumin and blood cells.

O'Hare et al. (112) in a series of 28 rabbits exposed the right kidney of a rabbit through an incision, to from two to ten times the erythema dose of medium wave lengths, following which the majority of the animals lived for from two to five months. One animal dying 24 hours after exposure, showed acute degeneration of the radiated kidney. The longer periods after exposure and higher doses showed chronic changes, with decrease in size of the kidney, thickening of the smaller arteries, gradual destruction of the tubules, thickening of Bowman's capsule; moderate amount of connective tissue reaction. In from three to four months there was a decrease in size of the kidney to half that of the control; marked sclerosis; vessels were thickened, tubules destroyed and undergoing degeneration; some capsular thickening of the glomeruli; sclerosis of some of the tufts and other changes; very prominent connective tissue increase and some cellular infiltration.

Hartman et al. (63, 64) using deep therapy found similar changes in young dogs, and in addition was able to bring about hypertension with a terminal stage of nephritis showing acidosis, vomiting, convulsions, coma, oliguria and anuria and marked nitrogen retention with the histological findings of a diffuse chronic nephritis with contracted kidney. Domagk (44) found atrophy of the tubules while the glomeruli were well preserved in rabbits.

Changes in the thoracic structures have not been found by many authors who have studied the effects upon patients (37) nor by those who have radiated the whole animal. Attempts were made by Warren and Whipple (157) to produce injury to the heart and lungs with large amounts of medium wave lengths without success. They produced large areas of skin desquamation by repeated and single exposures over the thorax and sacrificed the animals (dogs) at various intervals without finding appreciable injury. Muhlmann (107), described a girl of twelve who had a tumor in the right pleural region. She received a rather large amount of x-ray therapy over the tumor, and two and a half years later was found to have lack of development of the right breast and some infiltra-

tion of connective tissue into the lung on the right side. The left lung and left breast were normal for the girl's age. Another case cited was complicated by a tumor in the lung. Schweizer (147) describes a case of Hodgkin's disease in which the mediastinal structures received a large amount of radiation. There were marked changes in the lung, pleura, superior vena cava and the right ventricle, which was thought to be due to the radiation. Evans and Leucutia (53) thought that fibrosis of the lung with rather large doses of deep therapy was a natural consequence of the treatment, especially in post-operative treatment of carcinoma of the breast and other types of malignant disease of the chest. They have neglected to consider the usual sequence of events when carcinoma or malignant disease has metastasized to the chest, with the result, as pointed out by Desjardins (38) that the fibrosis usually present in later stages of this disease is not taken into consideration. Davis (32), in a good review of previous work, reported lesions in the lungs of dogs and rabbits with large amounts of medium wave length radiation—acute inflammatory changes characterized by edema and congestion of the lung parenchyma with later (5 to 7 months) fibrosis and often atelectasis of the radiated portion of the lung. The heart muscle, when in the field of radiation, showed swelling, tendency to fibrosis and hemorrhages. Dyspnea was noted in the experimental animals. Emery and Gordon (51) were unable to show by electro-cardiagraphic and microscopic study, any definite injury to the heart of rabbits within several months, nor were they able to show any changes by the same study of patients receiving a large amount of short wave length radiation over mediastinal and other tumors for a long time, which could be directly traced to the effect of radiation. Roffo (130) was unable to show any change in the development of the heart tissue cultures of the chicken embryo, either following soft or hard radiation in small or tremendous amounts. The cells retained their ability to grow and their normal embryonic appearance, up to amounts of 1100 milliampere minutes, at 200 K. V. This is contrary to the finding of injury to heart muscle in vivo by many experimentors in adult tissues.

Evidence of injury to thoracic structures therefore must be dependent on large dosage and sufficient elapse of time to allow the fibrosis and other changes to develop.

Zachel (165), investigating the "*roentgen cachexia*" through the mechanism of parabiosis, joined together the circulations of two white rats of about equal weight. He radiated one rat, using fairly short wave lengths, so that the animals died on the third or fourth day. The

temperature dropped consistently over the whole course of observation, but the drop was most marked during the periods of diarrhea, which occurred on the second day. The temperature was parallel, with slight variation, in the two animals from the time of radiation until death. The white count rose practically double the previous count three hours after radiation, and had almost returned to normal 8 hours after radiation, and there was a very marked drop over the succeeding days, the white count almost paralleling in the two animals from 8 hours after radiation till death. The radiated animal had a very marked diarrhea, as a rule; the unradiated animal no diarrhea. He concluded from this investigation of roentgen ray injury, that in the animal radiated certain toxic substances were elaborated which circulated in both animals causing their death. He gives a very good review of the subject and discusses the four series of hypotheses promulgated by Holthusen (71) as an explanation of the chronic intoxication following radiation.

These hypotheses represent, in the main, the chief theories at present under discussion concerning the mechanism of the intoxication manifested after radiation. The first, Holthusen designated as due to the change in the function of the glands of internal secretion as the cause for the onset of roentgen ray sickness. A second hypothesis was based upon the well-established changes in the mineral metabolism of the blood stream and the drop in chlorine content of the blood, with changes in the liver function, and apparently the serum proteins. The sodium chloride secretion of the kidneys was only a symptom of the upset in the equillibrium of the blood chloride, with also changes in the white blood count, urine protein, etc. The third hypothesis had for its foundation changes in the autonomic nervous system. Changes in the blood pictures were thought to be due to changes in the peripheral circulation influencing the vagus and the local innervation of organs; and due to indirect effect brought about by changes due to roentgen radiation in the skin parasympathetics. The fourth hypothesis stated that the elaboration of cell products from their death and injury by radiation, which products were probably protein digestive products, brought about the first changes of the roentgen-ray intoxication, and that these brought about various changes in the body corresponding with the nekrohormone hypothesis.

A case of generalized lymphomata reported by Warthin (159) well illustrates the widespread distribution of cellular debris following radiation. This case had received large amounts of heavily filtered deep therapy and showed, on death ten days later, a flooding of the

reticuloendothelium and phagocytic cells with chromatic detritus. With the destruction of large amounts of susceptible cells by radiation, sufficient protein could be broken down to toxic products which must be sufficient in quantity to cause the intoxication of the animal organism. A combination of the second and fourth hypotheses of Holthusen omitting the nekrohormones seems to be plausible. The supposed changes brought about in distant organs of internal secretion, the various parts of the nervous system, the effects of various hormones, etc., are not substantiated by any facts presented and are purely speculative explanations.

Claude Regaud (127), in a discussion of the latent period states that there is a certain relationship between the quality and the quantity of the radiation administered, which in turn also bears a certain relationship to the extent of the injury. In a review of the literature, he thinks that the sensitive cells of the epidermis are the generating cells of the basal layers, and that the changes in the skin occur as these cells are elevated upward toward the cornified surface. The period of latency is a measure of the time which is necessary for the "generation of cells" from the basal layer to reach the cornified stage in their progress upward towards the surface. The same is true of the testes, where the sensitive cells are the basal cells or spermatogonia. The adult sperm cells are relatively insensitive. Until time has passed to allow successive generations of cells to reach maturity, the injury is not apparent. This is the latent period for the spermatozoa. Thus, until sufficient time has elapsed for the maturation of the spermatogonia, the volume of the epididymis, which is the reservoir for the sperm, and the volume of the testes, does not decrease and it will not do so until that generation of adult sperm is due to arrive, which should have developed from those spermatozoids or spermatogonia which previously received the radiation. This latent period is more or less intermediate in type between the skin and the thymus. The thymus cells are very sensitive to radiation and the reduction in size of the organ becomes apparent in 48 hours, and therefore the latent period is very short, considered both from the macroscopic and microscopic manifestations. This latent period conforms to the interval of time which separates the death of these very sensitive cells, in this case the lymphocytes and the disintegration and absorption of the cell bodies. The crypt cells of the small intestine are midway between the gonads and the thymus in the duration of their latent period (3 to 4 days). Moderate injury with the production of atypical cells and changes in nutrition from injury to capillaries and connective

tissue cells may not show up for very much longer periods of time and give a false impression of the latent period. The appearance of telangiectases and skin changes sometimes a year or more after radiation is a reaction of this type (125). Matas (99) reported telangiectasia appearing four years after radiation.

A study of the effects of radiation with calibrated equipment and standardized measurements and careful elimination of the normal variables inherent in the use of various laboratory animals should enable us to correlate much of the data now available, and to clarify the many obscure factors preventing a clear concept of the fundamental changes brought about by radiation. This is a fascinating field for research, for it touches all branches of medicine and pathology in the study of the effects of radiation upon normal and abnormal cell function.

CONCLUSION

In conclusion, it must be emphasized that great confusion exists in the study of the effect of roentgen radiation upon body tissues, because of the lack of suitable standardized measuring devices, the absence of an easily established biological unit of dosage, and the failure of the various investigators to consider the variables introduced by the different wave lengths of radiation with their variation in penetration and absorption.

Radiation of the body tissues causes injury to cell structures and life processes, though the amount of injury produced is proportional to the amount of radiation administered at a particular wave length, and varies with the tissue radiated and, to a certain extent, with the species studied.

Moderate cell injury may be manifested by atypical cell division and development, with partial disturbance in function and organ structure. Pronounced cell injury is followed by cell disintegration with, of course profound disturbance in function and structure. The disintegration of cells after pronounced injury by radiation seems to be responsible for the intoxication present, and the changes found in the chemical constituents of the urine and circulating blood.

Almost infinitesimal amounts of the very longest wave lengths of radiation may be able to stimulate normal cells to an increased reproduction rate, (lymphocytes) with the production of normal daughter cells. The proof for a general stimulating effect of roentgen radiation is lacking at present.

The latent period seems to be that length of time necessary for the succeeding generation of cells to replace those present at the time of radiation or the time necessary for the injured cell to disintegrate. Both of these factors may be acting at the same time, so that disturbance in function or structure may depend upon whichever factor predominates and the extent of the cell injury.

The cells most sensitive to radiation seem to be the lymphocytes, the gonad cells and the epithelial cells of the small intestine. Secretory glands seem readily affected,—skin, bone marrow, connective tissue cells, muscle and capillaries somewhat less.

In short, if sufficient radiation is given to any particular cell type, the latter will be injured; and the effect upon the organism as a whole will depend upon the function of that cell type and the number of cells injured.

A great deal of information is lacking about the effects of radiation upon the body tissues, and the data which we have accumulated are difficult to correlate because of the great number of variables present.

A further consideration of the fundamental effects of radiation upon the normal cell and body structures would be controversial and based upon suppositions unwarranted at present because of the absence of sufficient data or proof.

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INDUSTRIAL FATIGUE IN RELATION TO ATMOSPHERIC CONDITIONS

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It is well known that atmospheric conditions have a considerable influence on the efficiency with which work is performed, whether the work in question is physical or mental. The present article deals with the performance of industrial work, which is mainly physical in character, for our information on this subject is greater and more exact than that relating to mental work; but there can be no doubt that much of the evidence described is to a greater or less extent applicable to both types of work.

Fatigue has been defined (11) as "the sum of the results of activity which show themselves in a diminished capacity for doing work." The information described below shows that in many instances the diminution in the capacity for doing work produced by fatigue is very considerable, so it follows that the more we can improve the conditions under which the work is performed the less will be the fatigue induced, and the more efficiently will the workers carry on their labour. Alternatively, the workers may continue to exert the same total expenditure of energy, and to fatigue themselves as much under the improved conditions as they previously did under the bad conditions; but they will have been able to work more rapidly and efficiently than before, and thereby have increased their productivity. By selecting the best conditions of work, we shall obtain a maximun production with a minimum of effort, and this is a most important consideration in these days of industrial unrest. It must be admitted that manual work, taken as a whole, is more monotonous than are mental pursuits, and if, in consequence of more efficient production a shorter working day is introduced, this will give the manual workers more leisure which they can, if they wish, devote to intellectual pursuits.

Of the numerous environmental conditions which influence industrial fatigue and efficiency, probably none are more important than atmospheric conditions, and these alone are dealt with in the present article;

but it is not for a moment implied that other factors are not equally worthy of study and consideration.

The atmospheric conditions considered. It is not proposed to discuss the effects of suspended impurities in the atmosphere such as dust and smoke, or of gaseous impurities such as carbon monoxide, for such matters form a special province of their own. Also the chemical composition of the atmosphere, more especially in relation to its content of carbon dioxide, will receive no mention, in spite of the importance attributed to it until comparatively recent times. Present day research has shown that though the carbon dioxide content of the air may occasionally afford a useful index of atmospheric pollution, it has no direct effect on industrial efficiency, and it is seldom that it gives us sufficiently valuable information to be worth the trouble of its estimation. The only factors of real importance relate to temperature, humidity and air movement. In addition to the dry bulb temperature, the wet bulb temperature has to be considered, and these two temperatures, taken in relation to one another, afford a measure of the relative humidity of the air, or its percentage saturation with moisture. As a rule it is necessary to consider the extent of the air movement in conjunction with the temperature, because of their close inter-relationship. It has been demonstrated by Leonard Hill, as the result of numerous investigations (4, 5), that for the purposes of controlling the heating and ventilation of rooms we need to know, not so much the actual temperature of the air as the *cooling power* it exerts on the body. This cooling power depends on the temperature and the air movement acting in combination, and Hill has invented an instrument, the *kata-thermometer*, whereby the cooling power may be measured.

The kata-thermometer. The kata-thermometer is an alcohol thermometer with a cylindrical bulb about 4 cm. long and 1.8 cm. in diameter, and on its stem there are two marks, corresponding to temperatures of 100° and 95°F. (37.8° and 35.0°C.). It is warmed to a temperature above 100°F. by immersing it in a vacuum flask of hot water, and after drying the bulb, the time required by the thermometer to cool from the upper to the lower temperature mark is taken by means of a stop watch. In order that the rate of heat loss may be expressed in heat units, the total heat loss (in milli-calories), when cooling between the marks, is determined for each instrument by the maker. This is divided by the surface area of the kata bulb expressed in square centimetres, and the figure so obtained, termed the *factor*, is marked on the instrument. Supposing, for instance, that the factor is 480, and it is found that the cooling time

of the kata is 80 seconds, then the cooling power of the air is 480/80 = 6.0. The cooling power ascertained in this manner is dependent partly on the actual air temperature and partly on the velocity of the air currents impinging on the bulb of the thermometer. By means of a formula (6), (22), (26) it is possible to calculate the velocity of these air currents, and the following sample data show various combinations of air temperature and air velocity which yield cooling powers of 6.0 and 7.0:

AIR TEMPERATURE	AIR VELOCITY WHEN COOLING POWER IS	
	6.0	7.0
	feet per minute	*feet per minute*
60°F. (15.6°C.)	10	24
65°F. (18.3°C.)	24	46
70°F. (21.1°C.)	52	89
75°F. (23.9°C.)	108	169

It will be seen that at a temperature of 60°F. (15.6°C.) the air has a cooling power of 6.0 when its velocity has the extremely low value of 10 feet per minute. If, however, the air is warmed to 75°F. (23.9°C.), it is necessary to increase the velocity to 108 feet per minute in order to obtain the same cooling power. If a cooling power of 7.0 is required instead of one of 6.0, the air velocities mentioned have to be increased to 24 feet and 169 feet respectively.

The cooling power exerted by the air upon the kata-thermometer is estimated at what is approximately the mean body temperature, and it is sometimes supposed that its readings can be applied directly to the cooling action which the air exerts upon the human body. This direct comparison cannot hold for several reasons. First the kata, by reason of its small bulk, exposes a relatively much larger surface to the air than the human body does, and secondly, it exposes an uncovered surface, whilst most portions of the human body are usually covered with clothing. Thirdly, as we shall see later on, the human body is constantly undergoing acclimatisation, which causes it to react differently to atmospheric conditions at different times and seasons. The only method available for calibrating the kata in terms of human sensation is by the laborious procedure of empirical graduation, and the writer, in conjunction with Bedford and Warner (23), has attempted this method by two series of observations. These observations were made in 12 large factories, where the workers were engaged in the manufacture of boots and shoes, machinery, tin canisters, polishes, etc. The atmospheric condi-

tions in these factories were investigated for periods of several months, both in summer and winter, and the workers themselves were frequently asked if they found the atmospheric conditions to be "comfortable," or "too hot," or "too cold." Altogether, 1,166 replies were obtained in winter (October to March), and 1,308 in summer (May to September). It will be seen from the table of results that a "comfortable" sensation of warmth was experienced by the workers in winter time when the air had a cooling power of 6.6, and in summer time when it had one of 6.4; whilst a rise or fall of about 0.8 unit caused the air to feel "too cold" or "too hot." Excluding the "much too cold" observations, because of

	Sensation experienced	Number of observations	Cooling power		Temperature	
			Mean	Difference from Summer	Mean	Difference from Summer
					°F.	°F.
Winter	Much too cold	32	9.1	(1.6)	51.1	(5.1)
	Too cold	145	7.9	1.4	57.1	5.6
	Comfortable	846	6.6	0.2 } 0.8	62.1	4.0 } 5.1
	Too warm	128	6.0	0.7	64.7	5.9
	Much too warm	15	5.3	0.8	68.2	5.1
Summer	Much too cold	1	(7.5)		(56.2)	
	Too cold	22	6.5		62.7	
	Comfortable	914	6.4		66.1	
	Too warm	248	5.3		70.6	
	Much too warm	123	4.5		73.3	

their small numbers, the others show an average cooling power of 6.5 in winter and of 5.7 in summer, whilst the last two columns of the table show that the air temperature at which a given sensation was experienced in summer was 5.1°F. (2.8°C.) higher in summer than in winter. That is to say, the sensation of warmth does not bear a steady relationship to cooling power, but varies with the seasons. This variation is due partly to the fact that less clothing is worn in summer than in winter, but also to the effects of acclimatisation. All of us are constantly undergoing some degree of acclimatisation as the temperature of the air rises and falls during each day and night, and a still greater acclimatisation as we pass from one season to another. The observations which we made in summer and winter upon ourselves (22) led to a similar conclusion. We paid special attention to the sensation of air movement, and we found that a "medium" sensation was experienced at a cooling power of

6.6 in winter and at one of 5.7 in summer, whilst the whole of the winter observations averaged 1.1 units higher than the summer ones. Arguing from these and other observations, we concluded that in factories suited for moderately light industrial work, the air ought to have a cooling power ranging from 7.0 in mid-winter to one of 6.0 in mid-summer (*cf.* 23). These values apply to Great Britain only, and would need to be modified for other countries which experience greater extremes of temperature.

In the observations described, no mention has been made of the wet bulb temperature and the humidity of the air. This is because the humidity is so steady in Great Britain that its variations are seldom sufficient to have a distinct effect on the sensations. In the 3,330 observations made by us in factories, the humidity was found to vary from 50 per cent to 69 per cent saturation in 77 per cent of all cases. Only in 1 per cent of the observations was the air more than 79 per cent saturated, whilst it was less than 50 per cent saturated in 5 per cent of the observations. However, high degrees of humidity produce a marked reduction of industrial efficiency, as will be shown later on, so it is important that the wet bulb temperature should be recorded. A combination of the effects of dry bulb temperature, wet bulb temperature and air movement can be ascertained by taking readings of the *wet* kata-thermometer. In this instrument the bulb of the *dry* kata-thermometer above described is covered with a muslin glove, which is wetted when the bulb is dipped in the flask of hot water. Owing to the evaporation of moisture from this wet covering, the wet kata cools about three times more rapidly than the dry kata, and its rate of cooling depends only on the wet bulb temperature of the air, and upon the air movement. However, the dry bulb temperature affects it indirectly, for it is well known that any rise of dry bulb temperature automatically raises the wet bulb. If, for instance, air saturated with moisture at 70°F. (21.1°C.) is warmed up till the dry bulb temperature reaches 80°F. (26.7°C.), the wet bulb temperature rises to about 74°F.(23.3°C.). In fact, each rise of 1° in the dry bulb temperature causes an automatic rise of about 0.4° in the wet bulb.

Effective temperature. The use of kata-thermometer readings for combining air velocity with dry and wet bulb temperatures into a single expression has hitherto not extended much beyond Great Britain and some of her colonies (especially South Africa). In America a different standard has been adopted, known as the *effective temperature.* In the research laboratory at Pittsburgh are erected two adjoining psychrometric chambers, the temperature and humidity of which can be varied in-

dependently between wide limits, whilst in one of the chambers air currents can be induced up to a velocity of 700 feet per minute. Different combinations of air temperature, humidity and air movement were established in the two chambers, and they were adjusted until the subjects, who stepped backwards and forwards from one chamber to the other, experienced the same degree of comfort or of discomfort. A large number of investigations were made by this method by Houghten, Yaglou, McConnell, Miller and others (7), (30), and charts were constructed from which it is possible to convert any combination of temperature and air movement into a single expression, called the effective temperature. A few of the results obtained with subjects at rest and normally clothed have been read off the chart and are recorded in the table. It will be seen that the effective temperature is considerably influenced by the humidity of the air. Still air at a given temperature and saturated with moisture has, by definition, the same effective tempera-

STILL AIR AT DRY BULB TEMPERATURE OF 65°F.			AIR AT DRY BULB TEMPERATURE OF 65°F. AND WET BULB OF 55°F.	
Wet bulb temperature	Effective temperature	Per cent saturation	Air velocity	Effective temperature
			feet per minute	
65.0°F. (18.3°C.)	65.0°	100	0	62.2°
60.0°F. (15.6°C.)	63.4°	73	100	59.9°
55.0°F. (12.8°C.)	62.2°	51	200	57.8°
50.0°F. (10.0°C.)	61.1°	36	500	53.5°

ture as the air temperature, but a reduction of the humidity lowers the effective temperature, and we see that air at 65°F., with a humidity of 51 per cent saturation, has an effective temperature 2.8° lower than saturated air.

The effects of high temperature at various humidities were amplified by observations on the rise of rectal temperature, the rise of pulse rate, the loss of body weight, and on other physiological reactions of the three subjects of experiment, when stripped to the waist. It was found that these reactions corresponded fairly well with the effective temperatures, but the writer has shown (20) that there is a distinct lack of agreement at low humidities.

It is obvious that the effective temperature method is more accurate than the kata-thermometer method above described, which is dependent on empirical graduations made at different times of the day and year, and with all sorts of variations in the clothing worn by the subjects of

experiment, and in other conditions. It has, however, one very great disability, as it makes no allowance whatever for acclimatisation. It is obvious that when a subject steps backwards and forwards from one chamber which may contain still air at a rather low temperature to the other chamber which contains moving air at a rather high temperature, he cannot be acclimatised to either set of conditions. He experiences the effects of the changes to a maximum degree, whereas, in ordinary life, we are almost always acclimatised to the air temperature to a greater or less extent, though apparently we do not get much acclimatised to variations of air movement. Now the kata-thermometer calibrations were made on ordinary individuals living under various temperature conditions to which they had got more or less acclimatised, and this fact of acclimatisation gives them their chief value. Because of its great bulk and its covering of clothing, the human body is theoretically much less sensitive than the kata to variations of air movement, and by contrast, is relatively more sensitive to variations of air temperature. In actual fact its sensitiveness to variations of air temperature is so much reduced because of acclimatisation, that its sensitiveness to air movement is, in comparison, rather greater than that of the kata (*cf.* 19, 31).

It follows that the chief test of the value to be ascribed to determinations of atmospheric conditions by the kata-thermometer and by the effective temperature method must depend on observations in the factory and in other places where industrial work is carried on, rather than in the laboratory.

The influence of radiant heat. So far it has been assumed that the exchanges of heat between the human body and its surroundings are effected entirely by convection currents of air, and by the cooling influence of the evaporation of moisture from the skin. There is, however, another factor to be considered which is always of some importance, and sometimes of very great importance, namely, the radiant heat from surrounding objects. According to Stephan's law, all bodies are radiating heat at a rate which varies as the fourth power of their absolute temperature. Hence the human body is usually radiating out more heat than it receives from surrounding objects, but the excess of such radiation varies greatly. We know that in rooms warmed by gas fires and coal fires the human body receives a large amount of heat directly from these radiant sources; but the point we more especially require information upon is the extent to which the industrial worker is affected by radiant heat. The so-called hot-water "radiators" which are frequently used for heating factories yield very little direct radiation, for it is calculated that, owing

to the heated columns obstructing one another, nine-tenths of their heat transmission to surrounding objects is effected by convection currents of hot air. Plenum air systems yield an even smaller proportion of radiant heat, whilst hot water pipes, especially if they run singly, give a considerably larger proportion. A system of heating known as the "panel" system is now coming into favour, in which concealed coils of narrow hot water pipes run in the ceiling or walls, and heat them to a temperature of about 100°F. (38°C.). The heat derived from these surfaces is mostly radiant, and the walls, ceiling and floor of the room (exclusive of the radiant surface) are about 3°F. warmer than the contained air, whilst with the other systems mentioned they are about 3°F. cooler than the contained air (*cf.* 25). This low-temperature radiant heat appears to have but very slight effect on the sensation of warmth experienced, but it causes the air to be warmed to an even temperature in all parts of the room. The temperature at floor level is slightly higher than at head level, whilst the other systems mentioned induce the less pleasant condition of a higher temperature at head level than at floor level.

The influence of high temperatures on efficiency. It will be convenient to describe first certain instances in which high temperatures and humidities were found to exert a pronounced influence on industrial efficiency, as we shall then be in a better position to decide whether the smaller atmospheric variations which are commonly experienced have any effect worth speaking of. The influence of high temperature is especially evident when the work is of a strenuous physical character, and the first instance to be described relates to coal mining. This industry employs over a million men in Great Britain, and four-fifths of these men work underground. When determining the influence of atmospheric conditions on efficiency, it is useless to rely on an output test, as the ease with which the coal is got varies so greatly in different working places owing to differences in the geological conditions. The writer, working with Bedford and Warner (24), made use of two tests which avoid this difficulty. The first depends on the fact that no man, when engaged on hard physical labour, is able to work continuously. Inevitably he takes short rests from time to time, and in very strenuous work these rests may add up to as much as 28 minutes per hour. Observations were made on 138 miners working at the coal face, and they were kept under observation for an average period of 96 minutes each. It can be seen from the table that the men working under the best atmospheric conditions investigated, rested on an average for 7.3 minutes per

hour, whilst those working under the worst conditions rested for 22.4 minutes. Moreover, the miners were not able to work so strenuously under the bad conditions as under the good ones, for we found that whereas they took, on an average, 8.0 minutes to fill each half-ton tub or wagon with coal when working under the best conditions, they took 9.6 minutes, or 20 per cent longer, under the worst conditions. Presumably they slowed down their rate of hewing coal and of doing their other jobs to a similar extent, and arguing on this basis, it is calculated that if the actual working capacity of the men under the best conditions is taken as 100, that attained under the worst conditions came only to 59. Now the worst conditions tested by us were not nearly so bad as those found in the hottest mines, where the temperature rises above 100°F. (38°C.), so we may safely say that under the worst conditions found in coal mines the efficiency of the men is not half as great as under the best conditions.

NUMBER OF MEN OBSERVED	TEMPERATURE		KATA COOLING POWER		AIR VELOCITY IN FEET PER MINUTE	EFFECTIVE TEMPERATURE	RESTS IN MINUTES PER HOUR	TUB-FILLING TIME IN MINUTES	EFFICIENCY
	Dry bulb	Wet bulb	Dry	Wet					
	°F.	°F.							
10	73.5	66.0	5.6	18.6	87	65.8°	7.3	8.0	100
16	70.1	65.6	4.8	14.6	34	65.8	6.7	8.6	94
17	81.7	73.6	3.1	12.9	46	75.3	9.0	8.5	91
47	80.8	74.1	2.8	10.8	25	75.8	10.0	9.2	82
42	82.4	76.2	2.4	9.0	18	77.8	11.1	9.1	81
6	86.2	79.3	1.7	6.4	10	81.2	22.4	9.6	59

The tabulated results are grouped in accordance with the *wet* kata cooling power of the air, and it can be seen that the associated dry kata cooling powers and the effective temperatures show more or less corresponding variations. When, however, the observations were grouped in accordance with the effective temperature, the associated variations in the rest pauses taken and in the tub-filling times were smaller and less regular, whilst the efficiency of the men in the successive groups of increasing effective temperature came to 100, 92, 94, 85 and 90 respectively. That is to say, the effective temperature scale appeared to be far less suitable an index of the atmospheric conditions than that provided by readings of the wet kata-thermometer.

The effect of air movement on the efficiency of the miners was shown by tabulating the results according to the air velocity. At a constant wet bulb temperature (75°F.) it was found that if the efficiency at the

highest velocities (71 ft. per min.) was taken as 100, that at a velocity of 33 feet per minute fell to 91, and that at one of 13 feet per minute, to 87.

These coal mining observations are in good agreement with the earlier observations made by Orenstein and Ireland (12) in a gold mine in South Africa. They put a native boy to work a rotary ergometer for four hours daily in working places at various depths, and they found that in air with a dry kata cooling power of 1, 2, 3, 4 and 5 his working efficiency was reduced by 50, 40, 30, 20 and 10 per cent respectively below that experienced in air with a cooling power of 6.

Other evidence indicating the effects of high temperature and of air movement on efficiency was obtained at tinplate works (16). In the manufacture of tinplate, slabs of steel, 20 to 40 pounds in weight, are heated to a bright red heat, and are rolled out thin by passing them a number of times between revolving iron rolls. The men have to manipulate the red hot slabs and sheets of steel by means of tongs, and are ex-

MONTH	MEAN OUTDOOR TEMPERATURE		MEAN OUTPUT	MONTH	MEAN OUTDOOR TEMPERATURE		MEAN OUTPUT
	°F.	°C.			°F.	°C.	
January	41.7	5.4	104.4	July	61.6	16.4	96.2
February	41.9	5.5	102.4	August	61.5	16.4	94.0
March	43.4	6.3	102.4	September	58.5	14.7	98.6
April	48.2	9.0	99.6	October	51.7	10.9	100.4
May	54.9	12.7	98.6	November	46.1	7.8	101.0
June	58.2	14.6	98.8	December	42.7	5.9	104.0

posed to the intense radiation from them. The weekly output of tinplate was ascertained at five factories over a period of 1½ to 7 years, and at every one of them there was a distinct seasonal variation in the rate of production. From the average data adduced, it will be seen that it was highest in January and December, the two coldest months of the year, and lowest in July and August, the two hottest months of the year. The extent of the variations observed differed greatly in the different factories, in accordance with the ventilation provided. At one factory, where there was a system of large paddles revolving immediately above the heads of the men, which churned up the air effectually, the summer output was only 3.0 per cent less than the winter output. At another factory, where air was blown down on the heads of the men (only a moderately good system, as the head and shoulders get too cold, and the legs are scarcely affected), the summer output was 6.4 per cent less, whilst at

two other factories, where no artificial ventilation was provided, the summer output was 11.0 and 13.4 per cent less.

Similar evidence of seasonal variations in output and of the effect of atmospheric conditions was obtained in a number of hot and heavy occupations in the iron and steel trade (17). In the production of cast iron, it is usual to load barrows with iron ore and coke till they sometimes weigh over a ton, and empty them into the top of the furnace. It was found that the rate of this furnace charging was 16 per cent less in the summer than in the winter. Steel is usually produced from iron by the open hearth process, and after the molten steel is drawn off the furnaces often need mending. The men have to approach within three or four feet of the open doors of the white hot furnace, and the work is terribly exhausting. In well ventilated works, however, no falling off was observed in the summer output, but in a badly ventilated works there was a fall of 11 per cent. The steel, after being cast into ingots, is rolled out into rails, girders, bars and sheets, and this rolling may necessitate a good deal of manipulation of the red hot steel by the men. In two works the summer output was found to fall off 9 to 13 per cent. Again, the wrought iron produced by the puddlers fell off 8 per cent in the summer.

The influence of humidity on efficiency. As has already been pointed out, the humidity of the atmosphere in Great Britain is such that the air in the factories is usually about 60 per cent saturated with moisture, and very seldom reaches a saturation of 80 per cent. Hence it seems probable that the efficiency of most industrial workers is but slightly influenced by the humidity. As the temperature rises, however, the effect becomes more pronounced, till at very high temperatures the humidity is of great importance. As the result of a large number of experiments on himself and other subjects, Haldane (2), (3) came to the conclusion that the maximum temperature which can be borne for some hours without the development of pathological symptoms such as heat stroke, depends on the wet bulb temperature. Neither the dry bulb temperature, nor the degree of humidity, nor the percentage of moisture in the air, matters of itself. Haldane found that in subjects who were stripped to the waist the endurable limit of wet bulb temperature was about 88°F. (31°C.) when resting, and about 78°F. (26°C.) when ascending steps at the rate of 14 feet per minute. In a current of air at a velocity of 150 feet per minute, the endurable limits were raised to 93° and 85° respectively. These observations were extended by the writer (5), who made parallel series of observations in comparatively dry air and in moist air. He

performed moderate mechanical work by step climbing at the rate of 13½ feet per minute (for 44 minutes in each hour), and it will be seen from the table that the endurable limit of wet bulb temperature was practically the same for dry and moist air when light clothing (shirt and trousers) was worn, and was likewise the same, though at a higher level, when no clothing was worn.

Houghten, Teague and Miller (8) made somewhat similar observations in their psychrometric laboratory, but they alternated 5-minute periods in which a fixed amount of mechanical work was performed, with equal periods in which they passed backwards and forwards between the two chambers, which were kept at different temperatures and humidities. They found that the sensation of warmth experienced by them was influenced by the dry bulb temperature of the air as well as by the wet bulb; but they did not investigate the maximum endurable limit of temperature, or the effect of atmospheric conditions on capacity for work, so their results are not in direct contradiction to those of Haldane and myself.

CLOTHING WORN	DRY AIR EXPERIMENTS		MOIST AIR EXPERIMENTS	
	Dry bulb	Wet bulb	Dry bulb	Wet bulb
	°F.	°F.	°F.	°F.
Light	90.2	80.8	81.8	80.9
None	98.3	85.9	87.1	85.7

The influence of humidity on industrial efficiency is of great importance in cotton weaving and linen weaving, for it is usual to humidify the air of the weaving sheds artificially (e.g., by blowing in steam) when weaving the finer kinds of cloth. The more moist the air and the higher its temperature the smaller is the tendency of the warp threads of the loom to break; i.e., the greater is the *physical* efficiency of the weaving process. On the other hand, the atmospheric conditions become more and more trying to the weavers, so that beyond a certain point the extra fatigue induced more than neutralises the physical potentialities of weaving, and the output falls off. This fact is well brought out by the following sets of observations made by Wyatt (29). In those recorded on the left side of the table, where the humidity was steady, it will be seen that as the dry bulb temperature rose above 74.9°F., the output deteriorated more and more, though the loom stoppages (due to breakages of the warp threads) diminished considerably. The observations on the right side of the table show that when the dry bulb temperature was steady, the

output rose when the relative humidity of the air was increased from a saturation of 76 per cent to one of 79 per cent, but fell away at higher saturations.

In other observations, Wyatt showed (28) that whilst, at temperatures up to 72.5°F. the output of the weavers kept nearly steady from hour to hour during the work spells, at higher temperatures it fell off more and more rapidly, according to the temperature. Again, Weston (27) found that in linen weaving the efficiency of the weavers during the afternoon spell of work was usually greater than in the morning spell, owing to the higher air temperature, but in hot weather it was distinctly greater during the cooler morning work spells. A wet bulb temperature of 73°F. (23°C.) appeared to be the optimum, above which the efficiency of the operatives was reduced owing to the adverse physiological conditions.

RELATIVE HUMIDITY 75 TO 80 PER CENT			TEMPERATURE 75° TO 80°F.		
Temperature	Loom stoppages per hour	Output	Relative humidity	Loom stoppages per hour	Output
°F.					
72.5 to 74.9	1.77	733	75.0 to 77.4	1.81	701
75.0 to 77.4	1.74	708	77.5 to 79.9	1.53	716
77.5 to 79.9	1.68	707	80.0 to 82.4	1.39	702
80.0 to 82.4	1.66	707	82.5 to 84.9	1.34	683
82.5 to 84.9	1.35	699			

It was shown by Wyatt that the adverse effects of the atmospheric conditions on weavers could be mitigated considerably by increasing the air movement in the weaving sheds through the introduction of electric fans. The warp thread breakages were not affected at all, but owing to the increased comfort experienced, the weavers were able to increase their production some 10 per cent on days when the air was very humid. The chief objection to the fans lies in their expense, but it is hoped that it may be possible to install a small fan at each loom, to be worked by the loom itself. This would cost very little, and every weaver could turn her own fan on or off, as she pleased.

The influence of moderate differences in atmospheric conditions on efficiency. It is very difficult to obtain accurate information on this subject, for the effects of moderate differences in atmospheric conditions are bound to be small, and such effects as there are may easily be hidden by the simultaneous operation of other factors. Nevertheless, the subject

is worth discussing. Ellsworth Huntington has treated it at considerable length in his book on *Civilisation and Climate*. His most reliable data relate to the workers in three factories where small metal articles such as brass fittings, hinges and screws were manufactured. He obtained information concerning the hourly output, in terms of wages, of over 400 piece-rate workers of both sexes for a four-year period, and these results, when averaged, showed a distinct seasonal variation. The rate of production was at a minimum in the latter part of January, when it attained a value of 89. It rose steadily to a value of 97 in June, and then fell to 94 in July-August. Subsequently it rose again to a maximum of 99 in November, and fell rapidly throughout December and the first half of January. Huntington ascribes these fluctuations to climate, and more especially to temperature variations. If the output is calculated in relation to temperature it appears that with the men the production rose steadily from a minimum of 96 when the outdoor temperature was lowest (20°F. or less), till it reached a maximum of 100 at 60°, and then it gradually fell to 98 as the outdoor temperature rose to 78°. The productivity of the women varied even more, as it gradually increased from 92 at a temperature of 25°F. or less to 98 at 60°. However, temperature cannot be the only factor, as is seen by comparing the output curve with the temperature curve. The air temperature reached a minimum in February, not in January, and rose steadily to a maximum in July, after which it fell steadily. When an air temperature of 40°F. was experienced in March the productivity was only 92, whilst at the same air temperature in November it was 98.

The comparable data obtained in Great Britain have not been worked out in the manner adopted by Huntington, but it is obvious that they differ from his results very definitely. The writer (18) collected output data of large groups of munition workers, some of them 90 to 100 in number, who were employed in fuse production. The nature of the articles manufactured and the conditions of production were unchanged throughout the 18 to 21 month period for which the output was observed, except in respect of the hours of work and the atmospheric conditions. None of these output data showed any fall whatever in the winter months though some of them did show a slight fall in August. Other output data (*cf.* 21) relating to groups of women engaged on various kinds of light repetition work, which were collected for continuous periods of 7 to 14 months, likewise failed to show any distinct seasonal variations. It must be admitted, however, that climatic variations in England are considerably less marked than those usually experienced in America, and in

winter time the outdoor temperature seldom falls below freezing point. In any case, the conditions under which Huntington's results were obtained are not described in sufficient detail to enable one to identify the cause or causes of the low winter output. For instance, nothing is said about the factory temperature. If this fell much below 60°F. (16°C.), the fingers of the workers would tend to get numbed by the cold, and there would, in consequence, be some loss of manual skill.

It must be concluded, therefore, that the seasonal changes of productivity observed in America cannot be attributed with any degree of certainty to climatic conditions, except for the small reduction observed at high temperatures, whilst in England the effect of climatic changes on production in light industrial work is so small that it cannot be definitely stated to exist at all.

The influence of atmospheric conditions on sickness and mortality. Atmospheric conditions not only have a direct and immediate effect in the production of fatigue, but they exert a cumulative action, which in course of time influences health and mortality. It is difficult to obtain clear cut evidence in support of this statement, as it is almost impossible to keep unchanged all the circumstances under which industrial work is performed, with the exception of atmospheric conditions. However, the effects are often so pronounced and so regular that there can be little doubt that they are due, for the most part, to the conditions in question.

The effects of atmospheric conditions on sickness and mortality are clearly seen among the men engaged on the hot and heavy work described in a previous section. In order to obtain evidence on the subject, Vernon and Rusher (17) tabulated the sickness and mortality data of 22,000 iron and steel workers for a six-year period. They found that all the groups of men engaged on hot and heavy work had a greater sickness rate than those working at ordinary temperatures, and the more strenuous the work the greater the sickness. Compared with the average sickness of the whole body of workers, the steel smelters showed a 23 per cent excess; the puddlers of wrought iron, a 20 per cent excess; the tinplate millmen, a 12 per cent excess, and the rolling mill men, an 8 per cent excess. The mortality figures more or less corresponded, for the steel smelters had a mortality which was 20 per cent in excess of that shown by the general male population of the country. The other groups had a smaller mortality, but all of them showed an excessive mortality from respiratory diseases, other than phthisis. In the steel smelters, the puddlers and the rolling mill men, it was 131 per cent above the average of the general male population.

Coal miners likewise show a considerable reaction to high temperatures. The comparative mortality figures (for men aged 25 to 65) issued by the Registrar General are recorded separately for the chief coal fields in Great Britain, and if we separate all these fields into two main groups, according to the average depth of the pits, we obtain the following comparison, for the years 1910–1912:

	COMPARATIVE MORTALITY FROM				
	All causes	Phthisis	Pneumonia	Bronchitis	Accidents
Shallow pits averaging 913 ft. (Nottinghamshire, Derbyshire, Northumberland, Durham)	599	64	43	32	74
Deep pits, averaging 1457 ft. (Yorkshire, Monmouth, South Wales, Lancashire)	825	86	79	66	144
Per cent increase	38	34	86	105	94

We see that the men working in the deep pit areas had a 38 per cent greater mortality, from all causes, than those working in the shallow pit areas. To what extent, if at all, can this increase be ascribed to atmospheric conditions? We see from the table that though the phthisis mortality showed a rather smaller percentage increase than the mortality from all causes, that from pneumonia and bronchitis was nearly twice as great. Presumably this was owing to the higher temperatures in the deeper pits. The men in the shallower pits would be working at a temperature of about 70°F. (21°C.), and those in the deeper pits at 79°F. (26°C.). They would, in consequence, get more overheated and perspire more freely, and would be more likely to catch chills on coming to the surface. In Great Britain it is very exceptional for the miners, when their work is over, to have a bath at the pithead and change into dry clothes. They proceed to their homes in their damp clothes, and so increase the risk of chills.

The effects of the smaller differences in the atmospheric conditions met with the average factory are naturally less marked than those observed in the hot and heavy industries, but nevertheless some effects do undoubtedly exist. For instance, Vernon and Bedford (23) collected sickness data, over a two-year period, of 809 women and girls engaged in making tin canisters. These workers were distributed in six large rooms, the atmospheric conditions of which were frequently tested. It will be seen from the table that the temperature of rooms *a* to *d* was similar,

being about 62°F. (17°C.) in the winter and 68°F. (20°C.) in summer. The amount of time lost from sickness was likewise similar, as it varied only from 1.47 to 1.64 per cent. Of the other rooms, room *e* was colder than the average, owing to a deficient heating installation, and in winter it was 7°F. colder than the other rooms. Apparently in consequence of this fact, the girls had a sickness rate of 21 per cent in excess of that observed in rooms *a* to *d*. Room *f*, on the other hand, was about 7° hotter than the average throughout the year, owing to the presence of a number of drying stoves. Apparently in consequence of this fact, the girls showed a sickness rate which was 32 per cent in excess of that observed in rooms *a* to *d*. It is impossible to be absolutely certain that the different sickness rates observed were due entirely to the differences in the

WORK-ROOM	MEAN WORKROOM TEMPERATURE				MEAN AIR VELOCITY		MEAN COOLING POWER		PER CENT OF TIME LOST BY SICKNESS	
	Winter		Summer		Winter	Summer	Winter	Summer		
	°F.		°F.		*feet per minute*	*feet per minute*				
a	59.8	61.7°	66.2	68.5°	40	47	7.9	6.6	1.47	1.55
b	63.0		67.2		32	37	6.8	6.0	1.51	
c	61.3		71.7		25	38	6.8	5.2	1.60	
d	62.5		68.7		21	28	6.3	5.5	1.64	
e	54.3		65.9		27	28	8.5	6.0	1.88	
f	67.1		77.9		35	33	6.0	3.7	2.05	

atmospheric conditions, for the various groups of girls were not engaged on the same occupations, though the work was light in every case. Nevertheless this evidence, coupled with the more substantial evidence described below, renders it extremely probable that the larger part of the effect was due to differences of temperature conditions. The girls kept their health best when the factory temperature was neither too high nor too low, but hit a happy mean.

The substantial evidence referred to relates to school children, and not to industrial workers, but it is permissible to apply it from the one group to the other. It was obtained by the New York State Commission on Ventilation, and it relates to a group of 2,500 children, who attended at eight schools, and a group of 3,000 children, who attended at 12 schools. The health of these children was carefully ascertained for periods of 8 and 12 weeks respectively in winter time, and during these periods the atmospheric conditions in their class rooms were recorded. For statistical purposes the rooms were grouped in three main divisions, namely:

A. 20 window-ventilated rooms (with gravity exhaust), kept at about 59°F. (15°C.)
B. 29 window-ventilated rooms (with gravity exhaust), kept at about 66.5°F. (19.2°C.)
C. 28 plenum fan-ventilated rooms (with gravity exhaust), kept at about 68.5°F. (20.3°C.)

On an average about 1 per cent of the children were absent from respiratory illness, whilst 6 per cent of those in attendance suffered from it. The children in the window-ventilated rooms at 66.5°F. did not differ noticeably from those in the window-ventilated rooms at 59°, but the children in the fan-ventilated rooms at 68.5°F. showed an 18 per cent excess in the number of absences, whilst of the children in actual attendance, 70 per cent more suffered from respiratory illnesses (chiefly colds and coughs).

The excess of respiratory illness in the fan-ventilated rooms was not due to overcrowding, for as a matter of fact the floor space averaged 14.7 square feet per pupil in them as compared with 11.1 square feet per pupil in the window-ventilated rooms. Nor was it due to deficient air movement, as this was rather greater in them than in the window-ventiated rooms. The Commissioners considered that the main factor responsible for the harmful influence of the fan rooms was high temperature, and in their final conclusions they state emphatically that "the avoidance of overheating is the primary essential in all systems of ventilation."

There is some reason for thinking that the temperature of 66.5°F., which was the average of the B. group of window-ventilated rooms, is too high for maximum health. Thus the absenteeism of the children from non-respiratory illness was 10 to 12 per cent greater in the children attending B. (and C.) rooms than in those attending A. rooms. Again, Louise Taylor-Jones (14), who studied the absenteeism in 15 public schools in Washington for a year, found that whilst the 445 eight-year-old children in the 14 schools with ordinary ventilation lost, on an average, from 1.1 to 3.5 days per year from colds, the 35 children attending the single open-window studied lost only 0.6 day from this cause. Exposure to too high temperature during school hours presumably renders the children less hardy and less resistant to infection. In regard to adults, Hubbard (9) points out that the air in the houses and offices in America usually has a temperature of 70°F. (21°C.) or more, but a relative humidity of only 20 per cent, and he states that in consequence of these atmospheric conditions Americans have become hypersensitive to draughts indoors, and to the weather variations outside.

The influence of atmospheric conditions on accidents. A portion of the sickness and mortality experienced by industrial workers is due to injuries and accidents, and in some heavy industries this portion is very considerable. The previously recorded mortality figures of coal miners show that in the shallow pit men accidents accounted for 12 per cent of the total death rate, and in the deep pit men, for no less than 17 per cent of it. In fact, the accident death rate was nearly twice as great in the deep pits as in the shallow ones, and it is important to determine whether this increase was due to the more adverse atmospheric conditions experienced. Evidence on the subject was collected by Vernon, Bedford and Warner (24), who investigated the accident rate of 3,000 miners for a six-year period. In one pit, separate data were obtained for the men working in a shallow seam, and in two portions of a deep seam. From the figures in the table it will be seen that whilst the men in the shallow seam suffered 57 accidents per 100,000 shifts worked, those in the upper

		SHALLOW SEAM	DEEP SEAM (UPPER)	DEEP SEAM (LOWER)
Atmospheric conditions	dry bulb temperature	64.6°F. (18.1°C.)	77.3°F. (25.2°C.)	81.4°F. (27.4°C.)
	wet bulb temperature	62.2°F. (16.8°C.)	71.6°F. (22.0°C.)	76.2°F. (24.6°C.)
	dry kata cooling power	5.7	3.4	2.7
	wet kata cooling power	15.2	11.3	10.2
Accident frequency		57	80	84
Accident severity		3.2	4.8	4.9
Mean depth of workings in feet		616	1,359	1,778

portion of the deep seam suffered 80 accidents, and those in the lower portion, 84 accidents. The accident severity rate (days lost per 1,000 hours worked) varied in similar proportion, and we see from the table that in correspondence with the increase of accidents the atmospheric conditions were considerably more adverse, for there was a rise of 14° to 17°F. in the wet and dry bulb temperatures. As it chanced, the physical conditions under which the coal was mined in the shallow seam were rather worse than those in the deep seam, so it seems reasonable to conclude that the effects recorded were really due to the atmospheric conditions.

Under the more adverse atmospheric conditions the men are apparently less ready to see and to avoid danger, and to take suitable precautions. Support of this statement is afforded by the observations of Davies (1) at the Morro Velho gold mine in Brazil. This mine is the

deepest in the world, the lowest workings being 6,000 feet below the surface. As may well be imagined, the atmospheric conditions were almost insupportable, so a cooling plant was installed, which reduced the temperature of the intake air to 43°F. (6°C.). In consequence, the wet bulb temperature in the lowest workings fell from 89°F. (32°C.) to 80°F. (27°C.), and the conditions became bearable. This improvement was reflected in the accident rate, for in the 16 months previous to the installation of the plant there were 20 fatal accidents, and in the 16 months after its introduction, only 6. Incidentally, the total output of the mine went up 12 per cent, as the men were able to work more efficiently.

Atmospheric conditions affect the frequency of minor accidents no less than of major accidents. During the great war Mrs. Osborne and the writer (13) determined the frequency with which such accidents were incurred at three large munition factories over a period of 6 to 12 months. The temperature of the workrooms was recorded continuously by means of thermographs, and the following data show the relative accident frequency at various air temperatures (in °F.).

	49° or less	50° to 54°	55° to 59°	60° to 64°	65° to 69°	70° to 74°	75° or more
Men	132	137	114	106	100	102	139
Women	132	134	119	107	100	107	107

It will be seen that both men and women attained a minimum accident frequency at a temperature of about 67°F. (18°C.). At higher temperatures the frequency increased rapidly in the men, and slowly in the women. The men were engaged on much heavier work than the women, and probably felt the heat more in consequence. The accident rise experienced at lower temperatures was probably due to loss of manual dexterity, as the workers were continually touching the metal shells and fuses they were making, and much of their work was done with wetted hands.

CONCLUSION

The evidence adduced is sufficient to show that atmospheric conditions have a considerable influence upon industrial health and efficiency, especially in the hot and heavy trades, and in processes such as weaving. The available evidence is often meagre, and is sometimes wanting in accuracy owing to the very great difficulty of excluding variations in the conditions of work, other than the atmospheric conditions under investigation. Frequently it is necessary to collect laboriously masses of

statistical material, and analyse them critically, before reliable conclusions can be drawn. Nevertheless, the information already obtained is sufficiently valuable to warrant a more extensive and thorough attack upon the numerous problems above referred to, and upon other related problems which have been omitted for lack of adequate information.

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